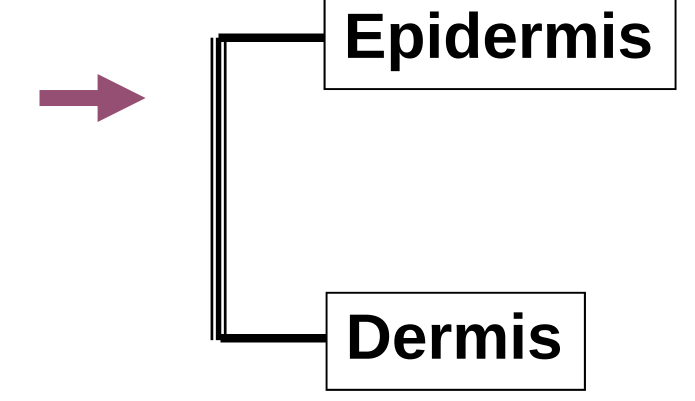
Biochemistry of Skin

Assoc.Prof.Siriwan Ongchai, Ph.D

Department of Biochemistry,
Faculty of Medicine,
Chiang Mai University.

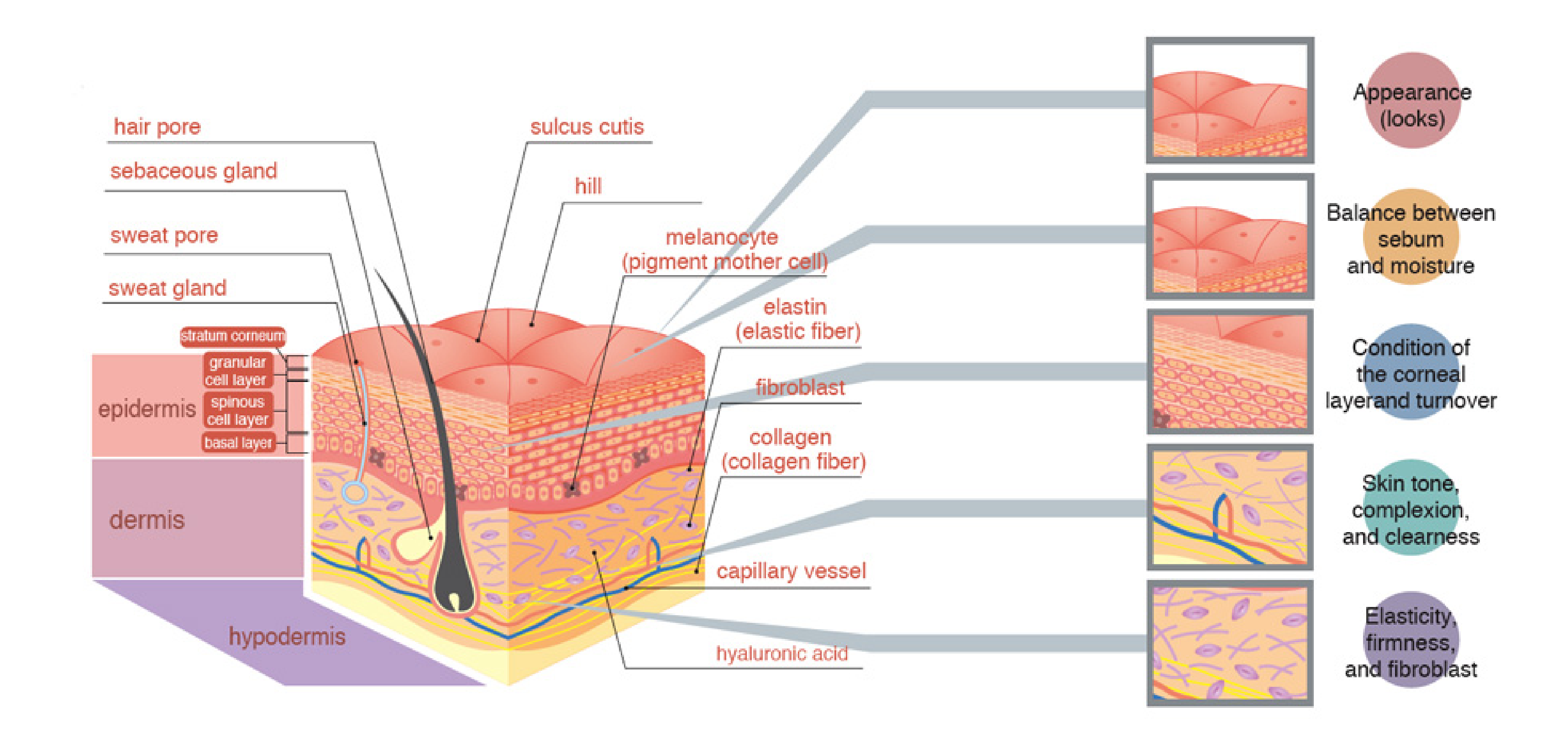
Objective

- Structure and Function of skin biomolecules



- Skin junction and diseases
- Skin Melanogenesis: mechanism and functions
- Skin Melanognesis and associated disorders
- skin ageing
- Nutrition and skin

Functions of Skin



Functions of Skin

Protection:

Sensation:

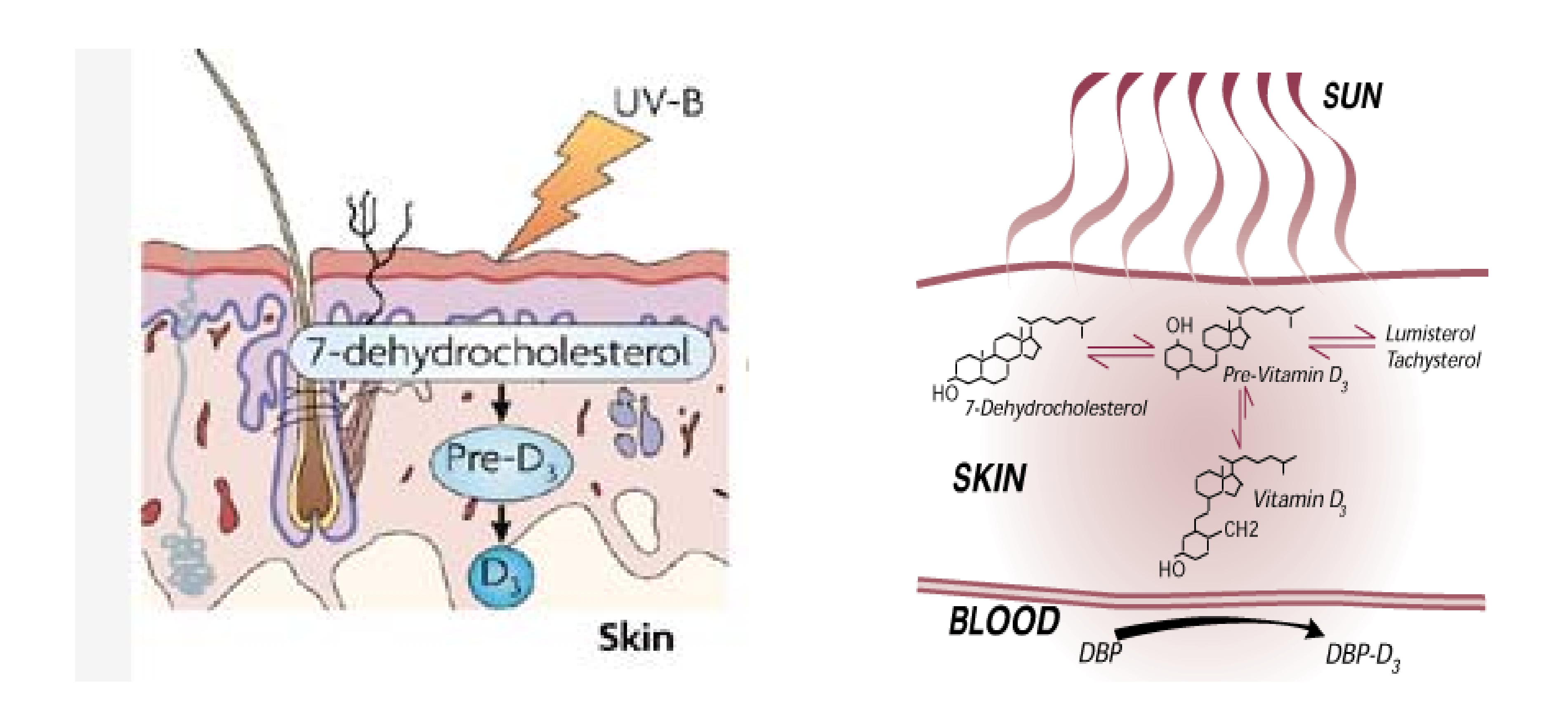
Heat regulation:

Control of evaporation:

Storage and synthesis:

Excretion: **Absorption**:

Water resistance:



This figure shows the conversion of 7-dehydrocholesterolto vitamin D in the skin and its transfer to the blood where it is complexes to a Vitamin D binding protein (DBP).

Epidermal Biomeolecules

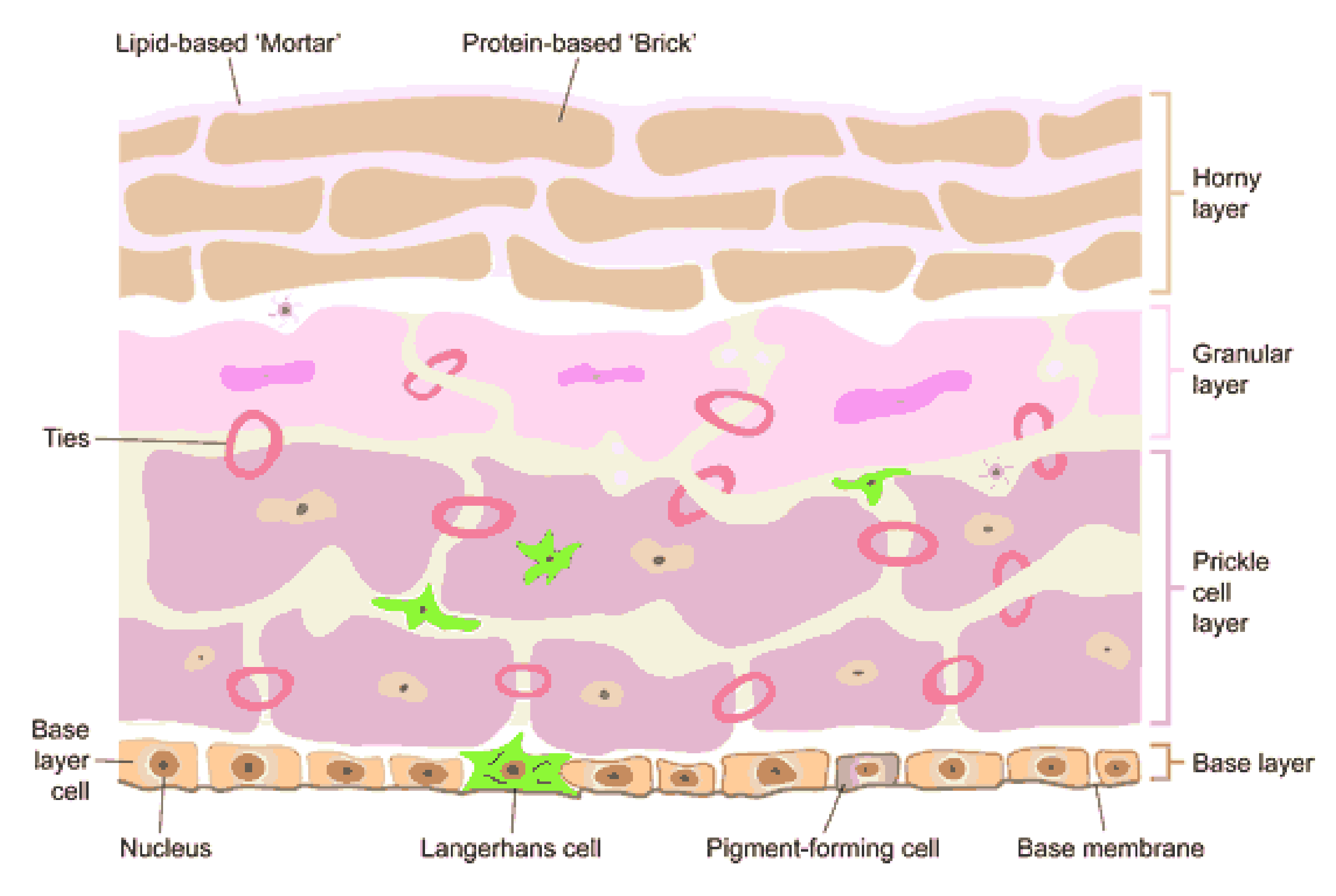
Intercellular spaces between keratinocytes

Lipid leaflets (barrier lipid) → **Glycolipids, Sterols, Phospholipids**

Proteoglycans →

Epican; HS/CS proteoglycan,

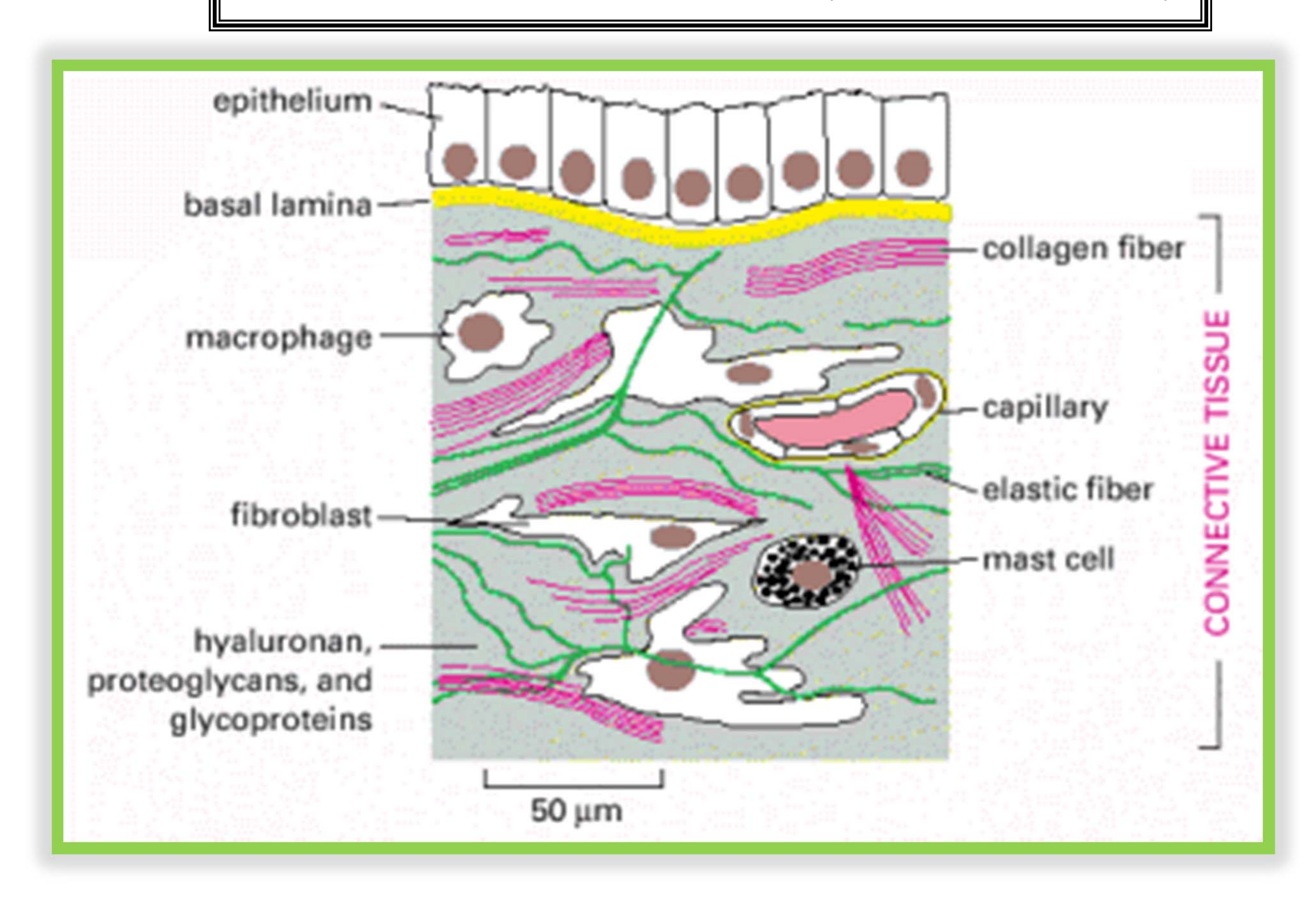
Epican is a heparan/chondroitin sulfate proteoglycan form of CD44 and is expressed on the surface of keratinocytes from the basal layer to the granular layer of the epidermis.



One way to understand the barrier function of the stratum corneum is to consider it as a brick wall. The corneocytes (made of tough protein) form the bricks and between these a double layer of lipids (fatty materials) and water make up the mortar. Some lipids have a hard crystal-like structure and are impermeable to water. Others lipids do not have this structure and they allow water to percolate through. So, the barrier is semi-permeable.

http://www.hse.gov.uk/skin/professional/causes/understand.htm

Dermal Biomeolecules (Dermal ECM)



Dermal Biomeolecules (Dermal ECM)

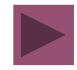
Fibrous protein:
- **Collagens**
- **Elastin**

Ground substance:

Glycosaminoglycans → Hyaluronan

Proteoglycan
- Small DSPG
- Large CSPG

Glycoproteins and enzymes; MMPs



Dermal collagens: a major component of skin

type I ~ 85-90%

type III ~ 8-11% (more prominent in fetal skin and early stage of wound healing)

type V ~ 2-4%

small proportions; type VI, XII, XIII

10 Only gly
Pro easy
7 Only gly
4 Only gly
1 Only gly

64 nm

(a) (b) (c) (d) (e) (f)



Collagen peptide

It is also called collagen hydrolysate, gelatine, gelatine hydrolysate and hydrolyzed gelatine.

Collagen peptide biological activities

Bovine hide CH(GELTA® CPB1000) stimulated cell proliferation, *HAS2* mRNA expression and hyaluronan production in human dermal fibroblasts

J Dermatol. 37(4): p. 330-8.

After 4 weeks of daily ingestion of CH, it promoted stimulatory effects on skin tissue, increasing expression levels of type I and type IV collagen

J Med Food. 14(6): p. 618-24.

Collagen hydrolysate ingestion inhibited ultraviolet B-induced decreased of type I collagen, thus improving skin conditions in mice

Biosci Biotechnol Biochem, 2009. 73(4): p. 930-2.

Side Effects of Taking Collagen Supplements

- **High Calcium Levels** → hypercalcemia.

Too much calcium in the body causes constipation, bone pain, fatigue, nausea, vomiting and abnormal heart rhythms.

- **Hypersensitivity Reactions** → abnormal response of the immune system against allergens

Dermal Biomeolecules (Dermal ECM)

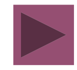
Fibrous protein: → **Collagens**, **Elastin**

Ground substance:

Glycosaminoglycans → Hyaluronan

Proteoglycan → Small DSPG, Large CSPG

Glycoproteins and enzymes; MMPs



elastic fiber

STRETCH

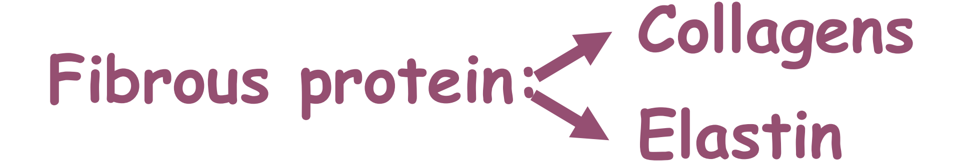
RELAX

single elastin molecule

cross-link



Dermal Biomeolecules (Dermal ECM)

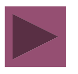


Ground substance:

Glycosaminoglycans → Hyaluronan

Proteoglycan → Small DSPG; → Large CSPG

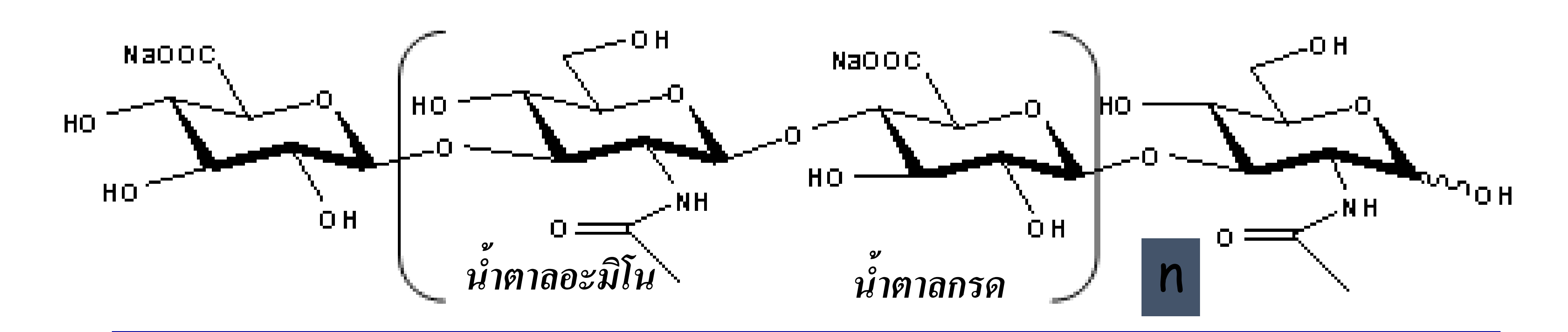
Glycoproteins and enzymes; MMPs



Glycosaminoglycans (GAGs)

*Jelly-like property

* Heteropolysaccharide

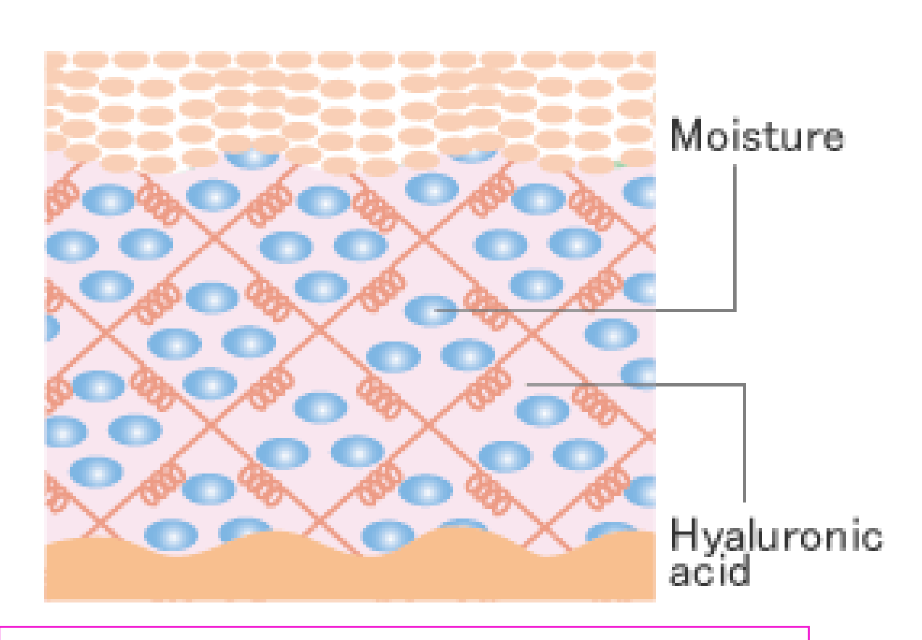


*No sulfate in the chain

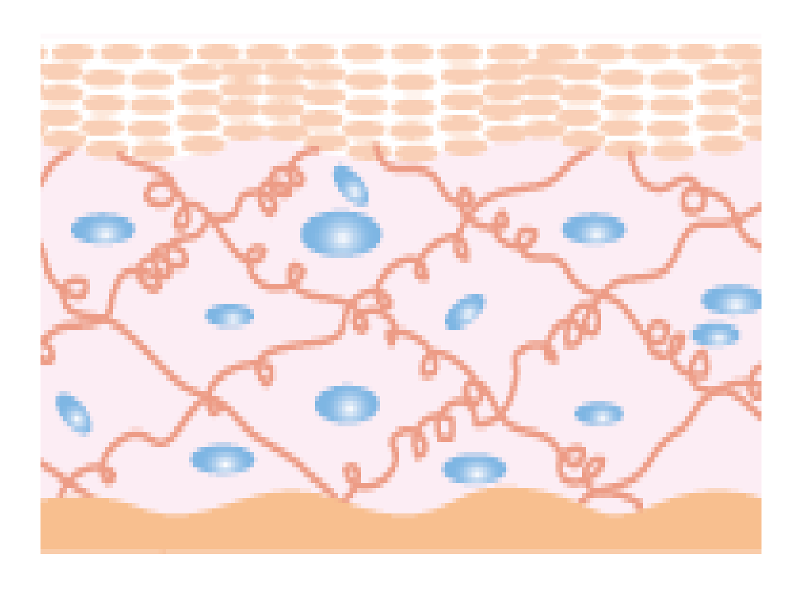
*No covalent bonding with protein to form proteoglycan

* High content in child and gradually decrease with age

Loss of HA associated with skin aging



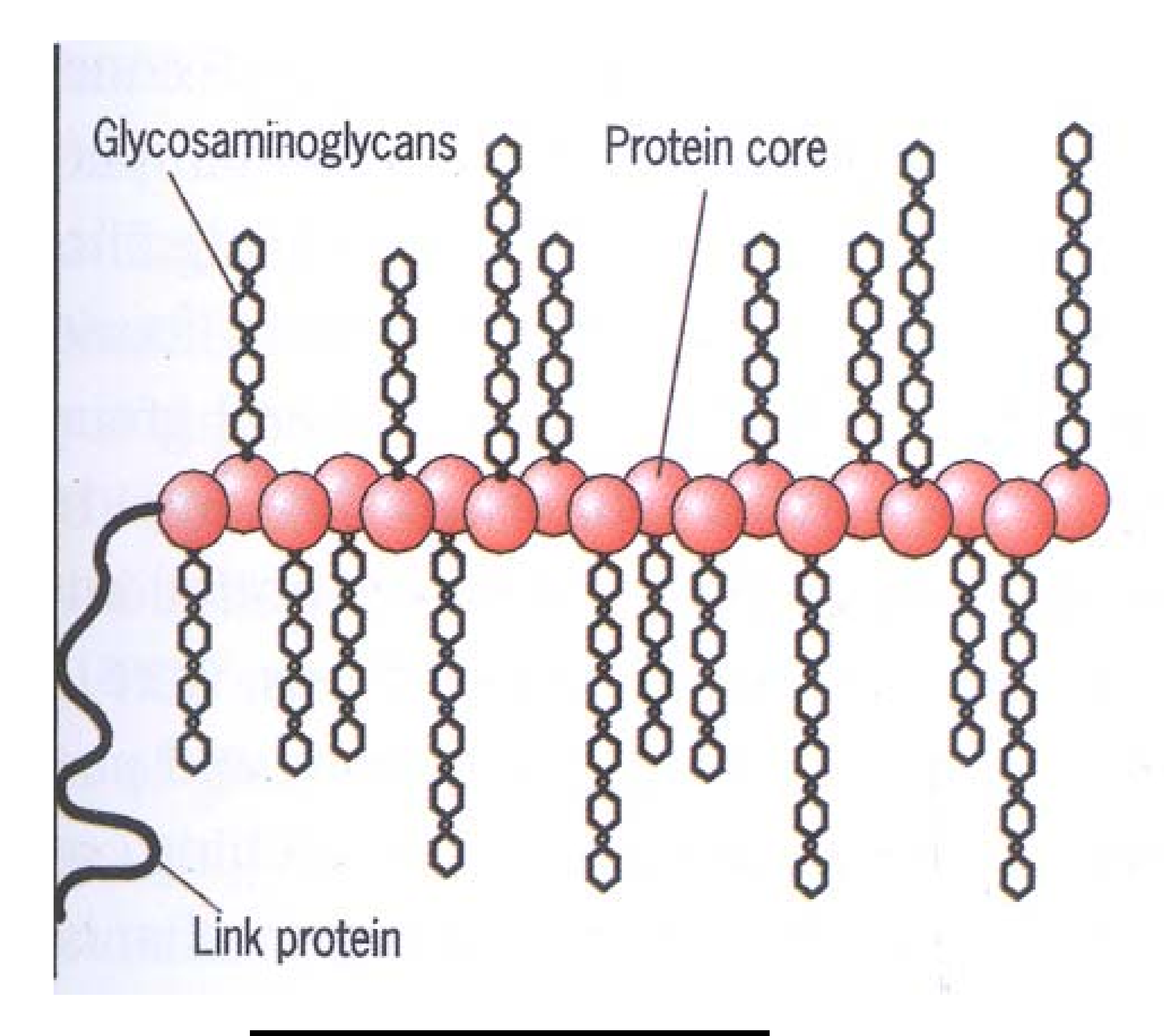

Skin with high HA content



Skin with low HA content

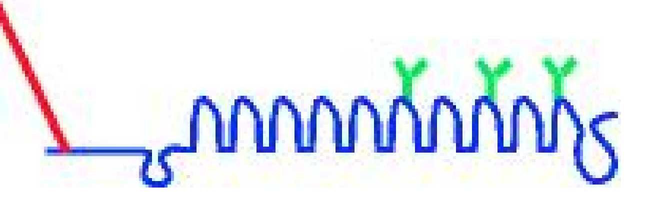
Bacterial Hyaluronidase

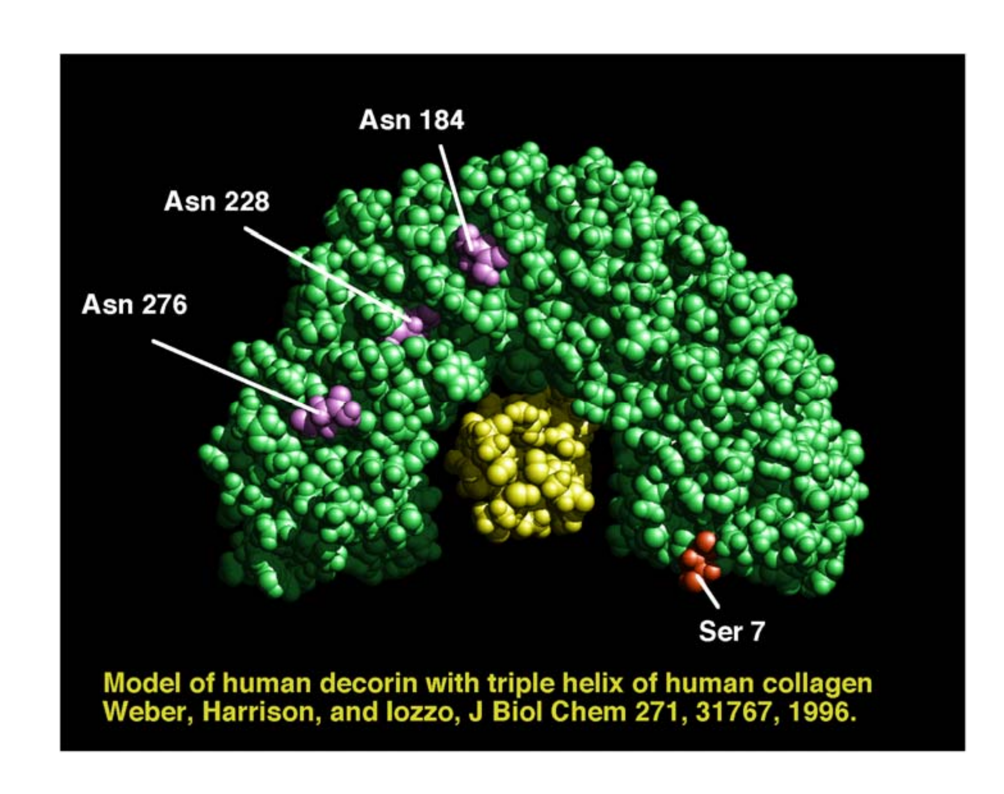
Bacterial hyaluronidases, enzymes capable of breaking down hyaluronate, are produced by a number of pathogenic Gram-positive bacteria that initiate infections at the skin or mucosal surfaces.

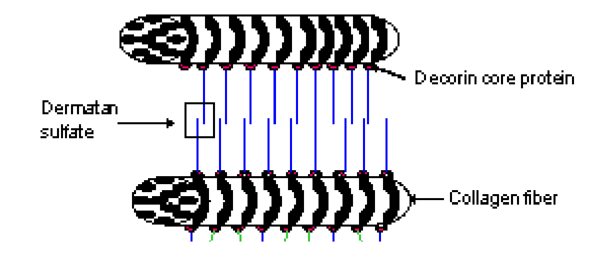


Proteoglycan)

Decorin



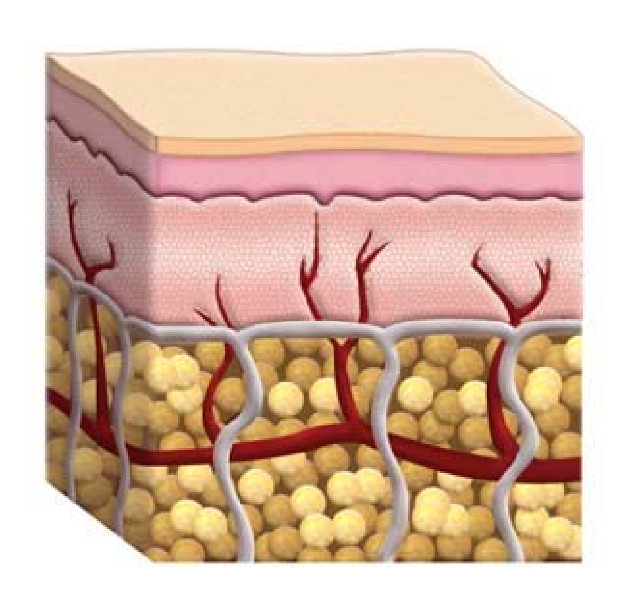

Asn 184
Asn 228
Asn 276
Ser 7
Model of human decorin with triple helix of human collagen
Weber, Harrison, and Iozzo, J Biol Chem 271, 31767, 1996.


Decorin core protein
Dermatan
sulfate
Collagen fiber

Decorin knock-out mice



Hypodermis



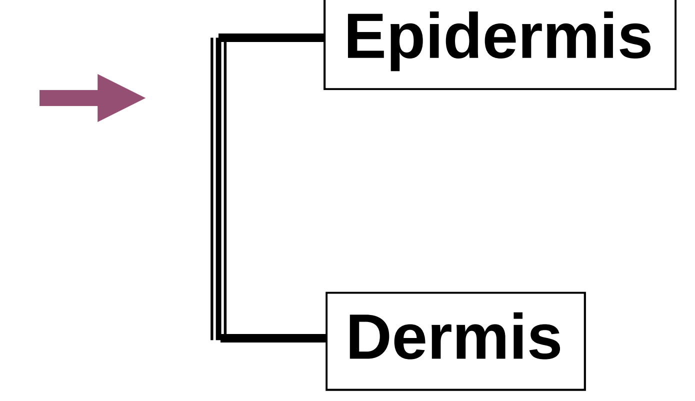
The hypodermis is the innermost and thickest layer of the skin. It invaginates into the dermis and is attached to the latter, immediately above it, by collagen and elastin fibres.

It is essentially composed of a type of cells specialized in accumulating and storing fats, known as adipocytes.

These cells are grouped together in lobules separated by connective tissue .

Objective

- Structure and Function of skin biomolecules



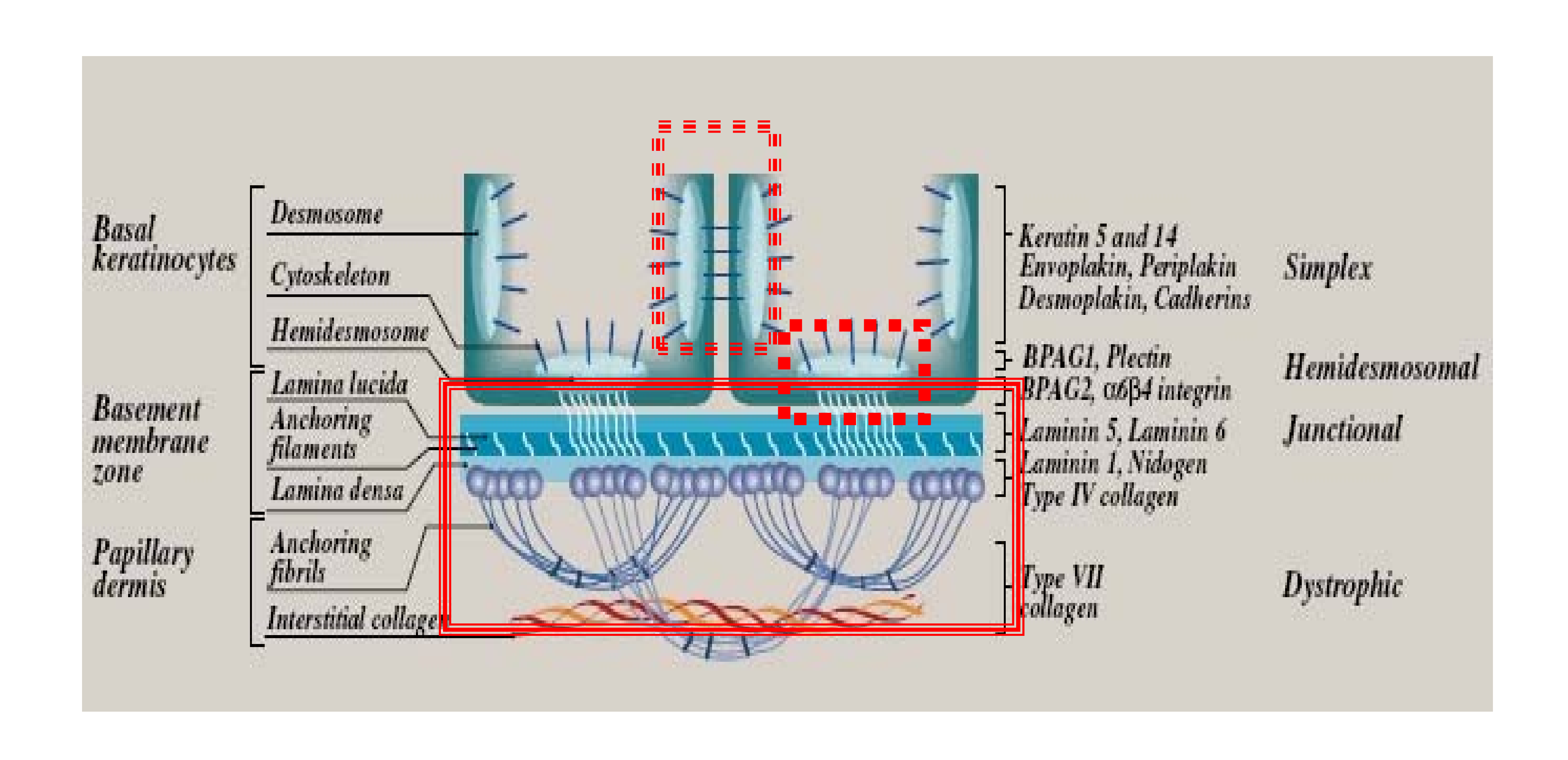
- Skin junction and diseases
- Skin Melanogenesis: mechanism and functions
- Skin Melanognesis and associated disorders
- skin ageing
- Nutrition and skin

Skin Junction

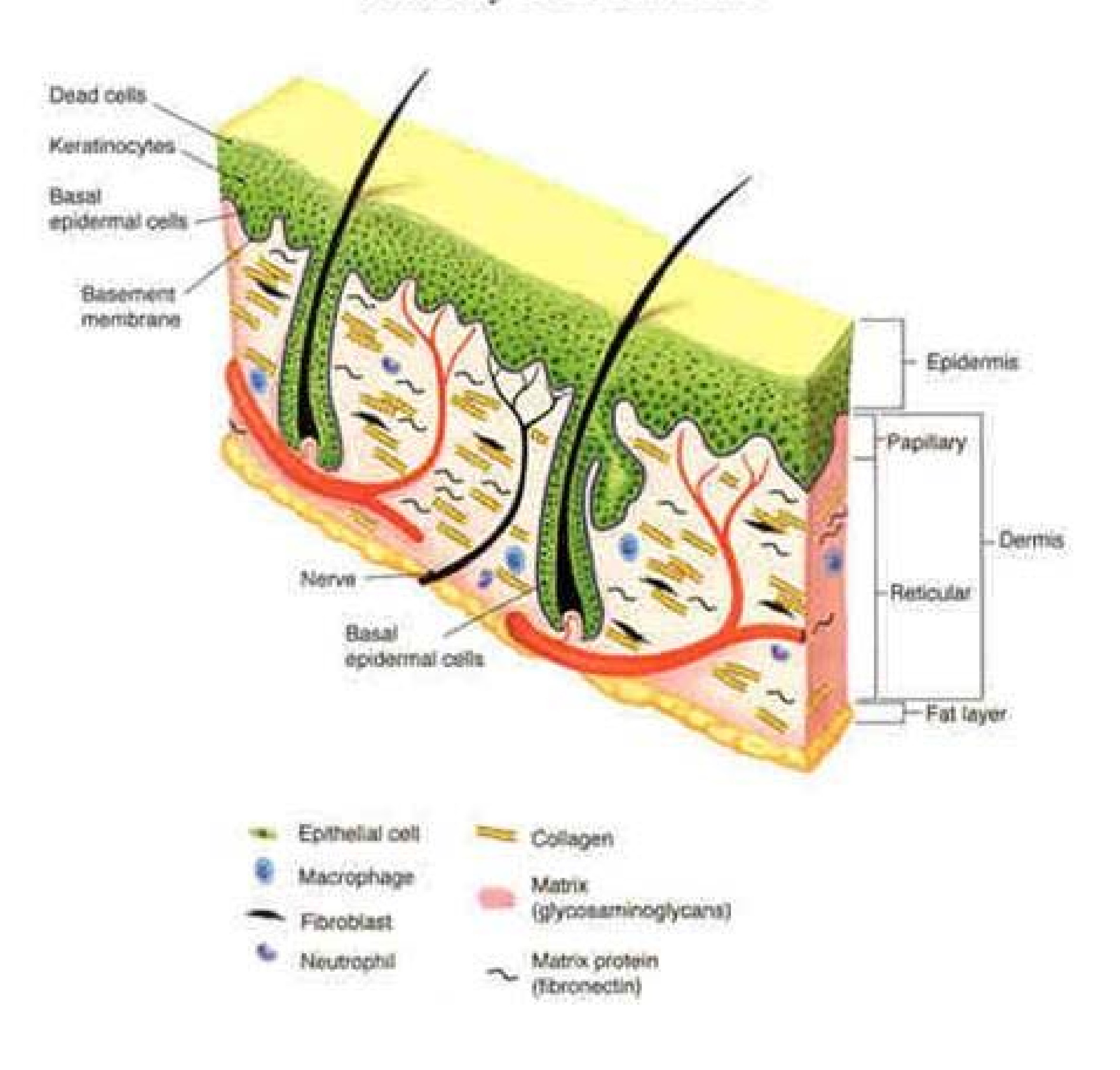
- Dermoepidermal Junction

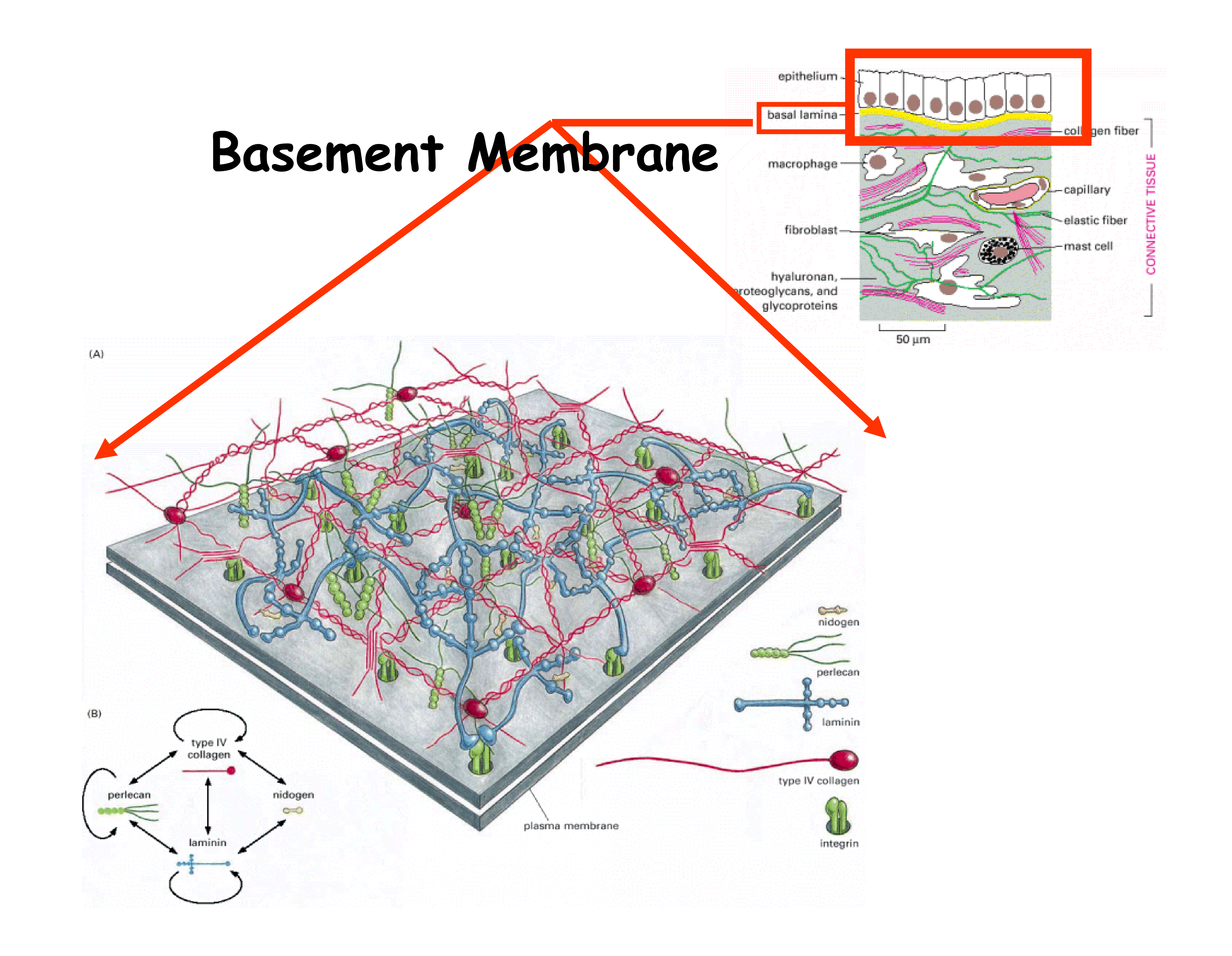
- Hemidesmosomal Junction
- Desmosomal Junction

Skin Junction

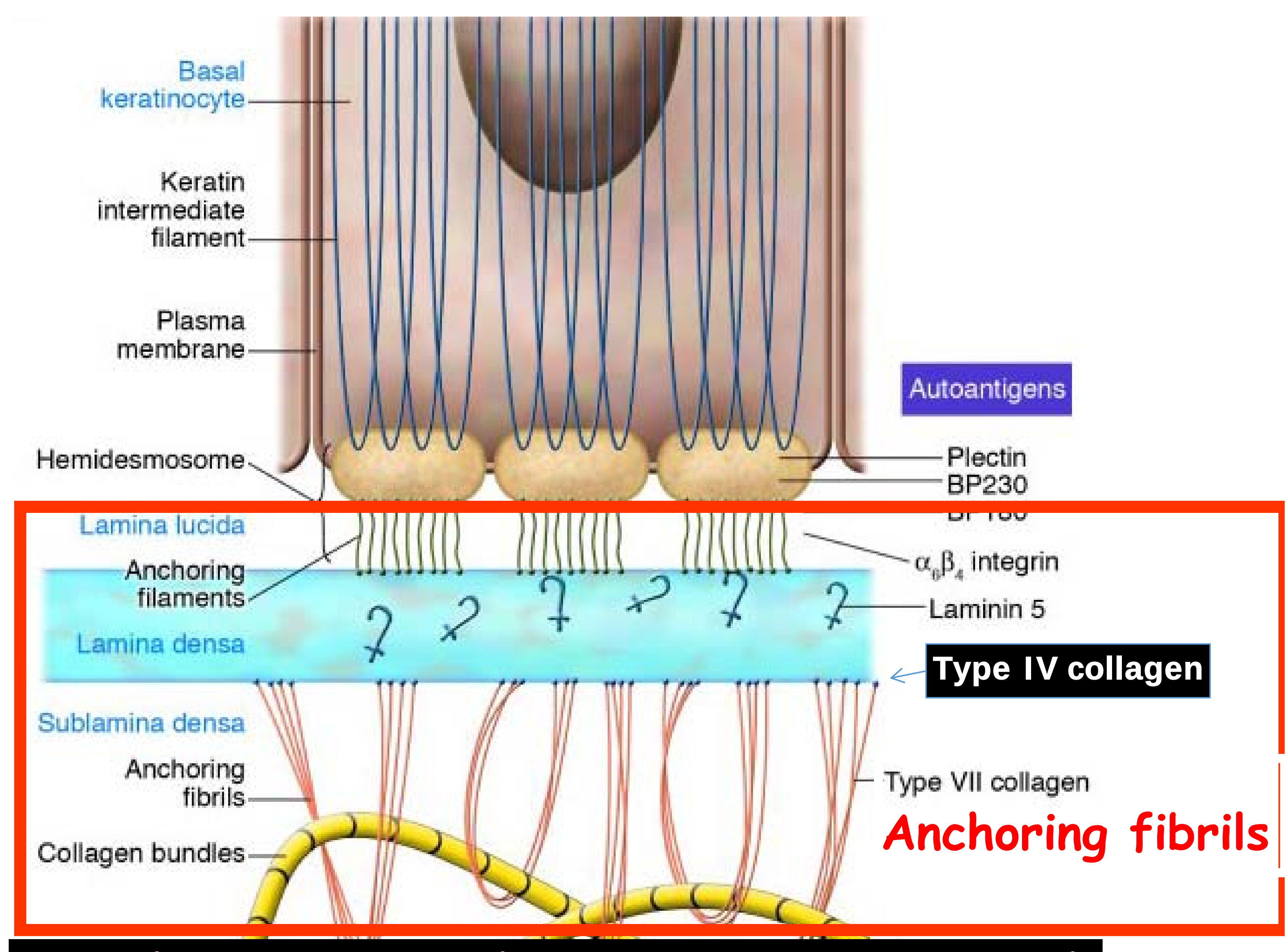


Dermoepidermal Junction





Basement Membrane
epithelium
basal lamina
coll gen fiber
macrophage
capillary
elastic fiber
fibroblast
mast cell
hyaluronan,
roteoglycans, and
glycoproteins
CONNECTIVE TISSUE
50 µm
(A)
nidogen
perlecan
laminin
type IV collagen
integrin
plasma membrane
(B)
type IV
collagen
perlecan
nidogen
laminin



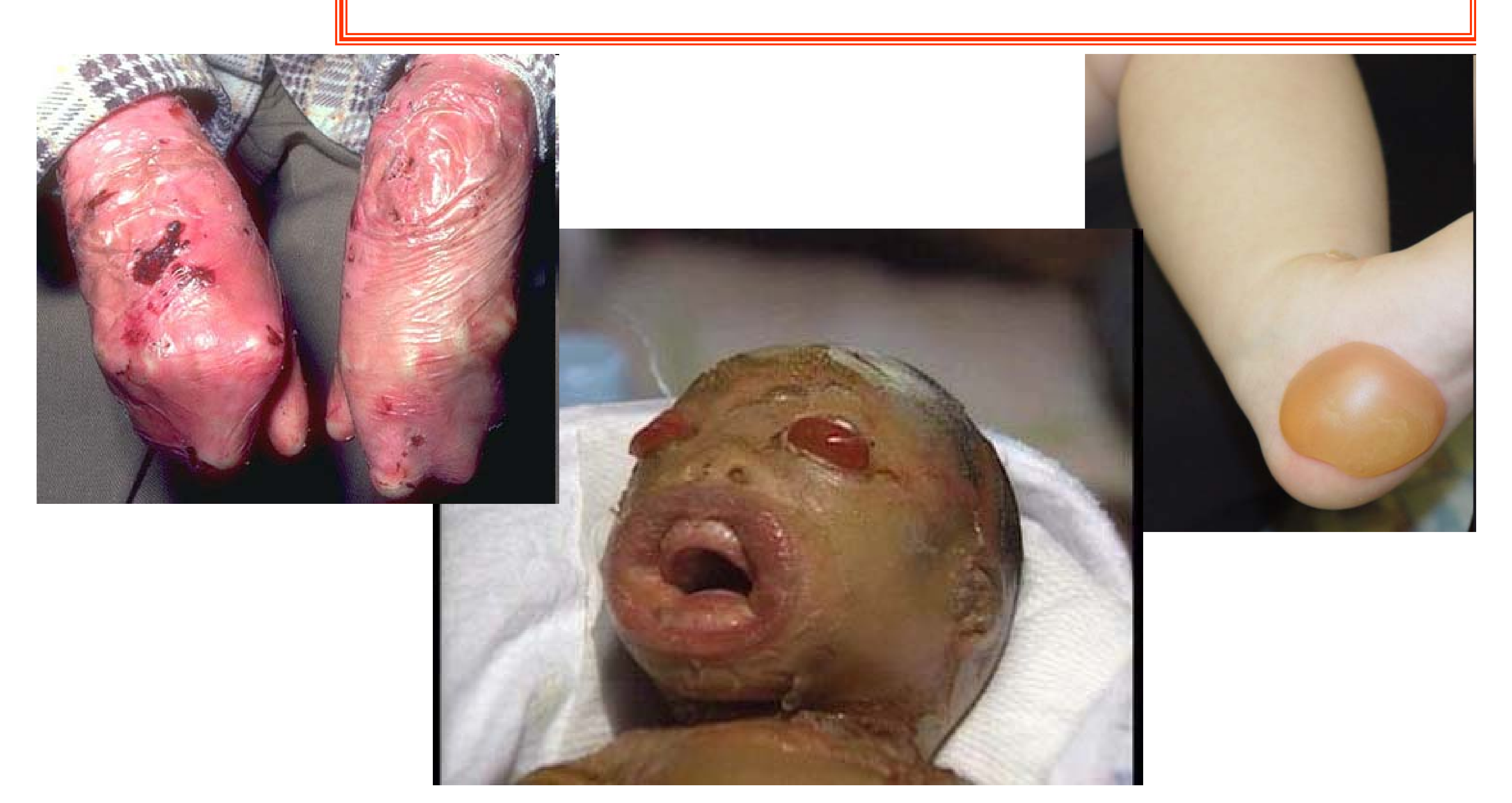
Basal membrane (Basement Membrane)

Epidermolysis bullosa dystrophica (Dystrophic EB; DEB)

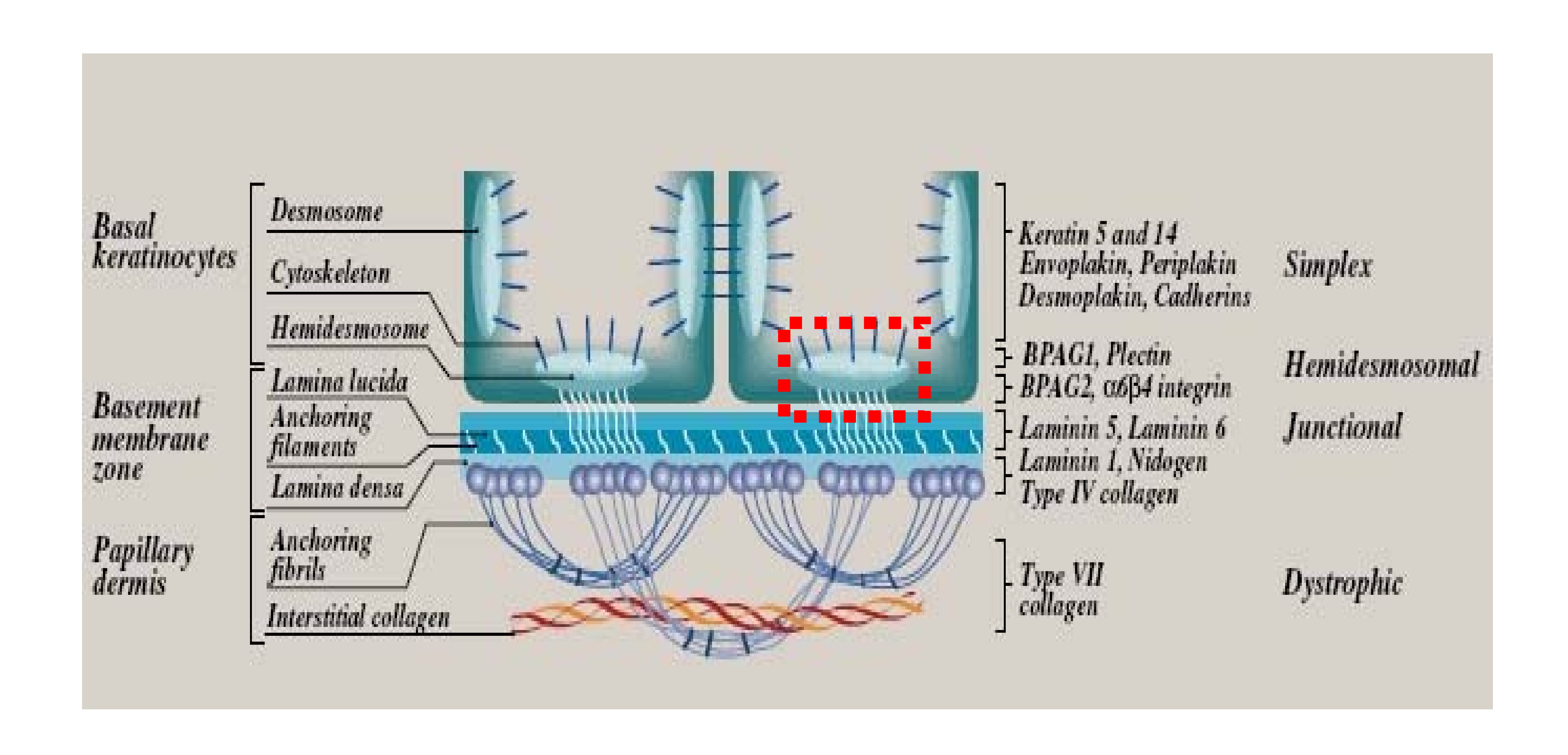
- **The deficiency in anchoring fibrils impairs the adherence between the epidermis and the underlying dermis.**

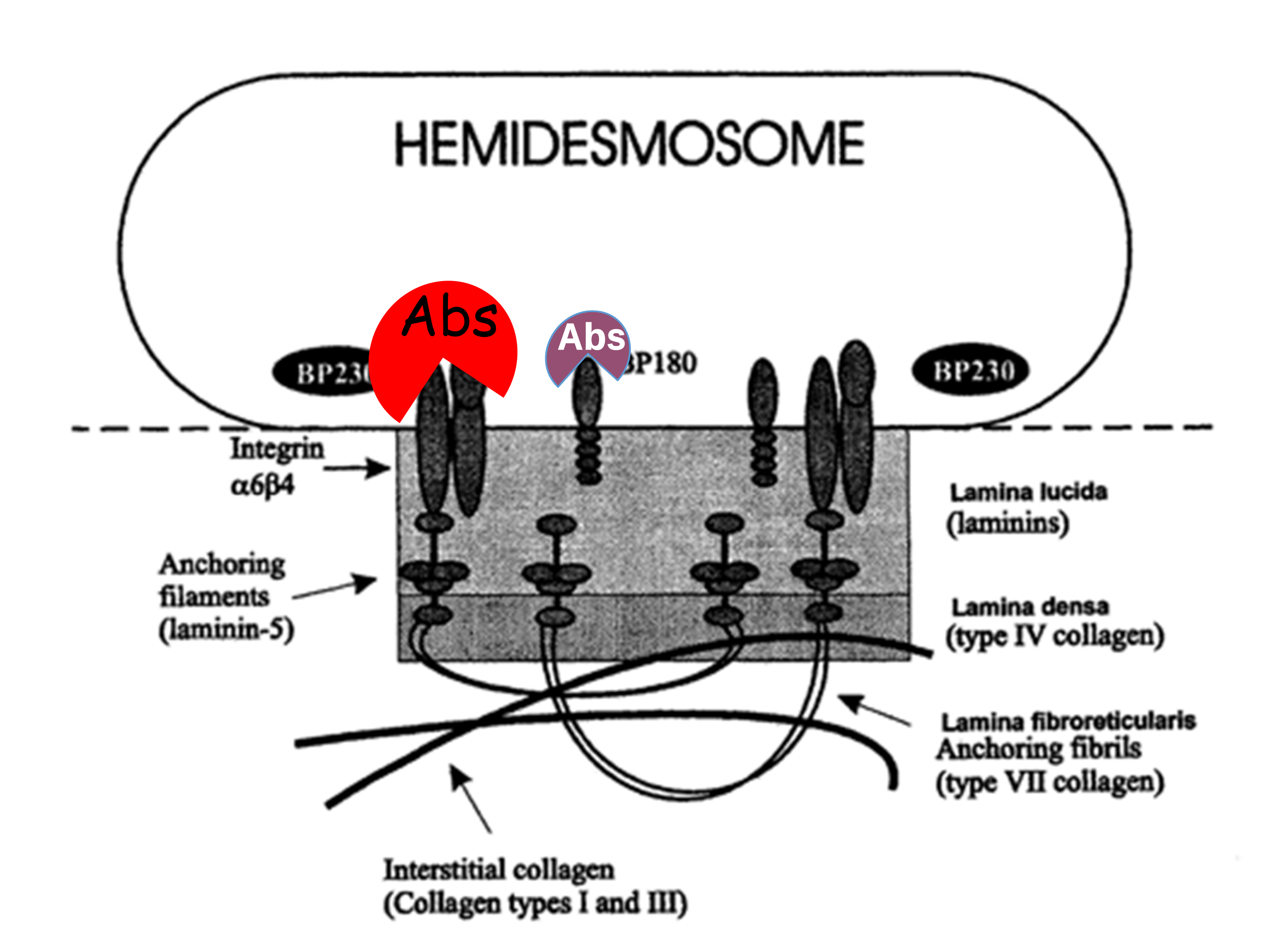
- **The skin of DEB patients is thus highly susceptible to severe blistering.**
- **Open wounds on the skin heal slowly or not at all, and are particularly susceptible to infection.**
- **The chronic inflammation leads to errors in the DNA of the affected skin cells, which in turn causes squamous cell carcinoma (SCC). The majority of these patients die before the age of 30.**

Epidermolysis bullosa dystrophica
(Dystrophic EB; DEB)



Skin Junction



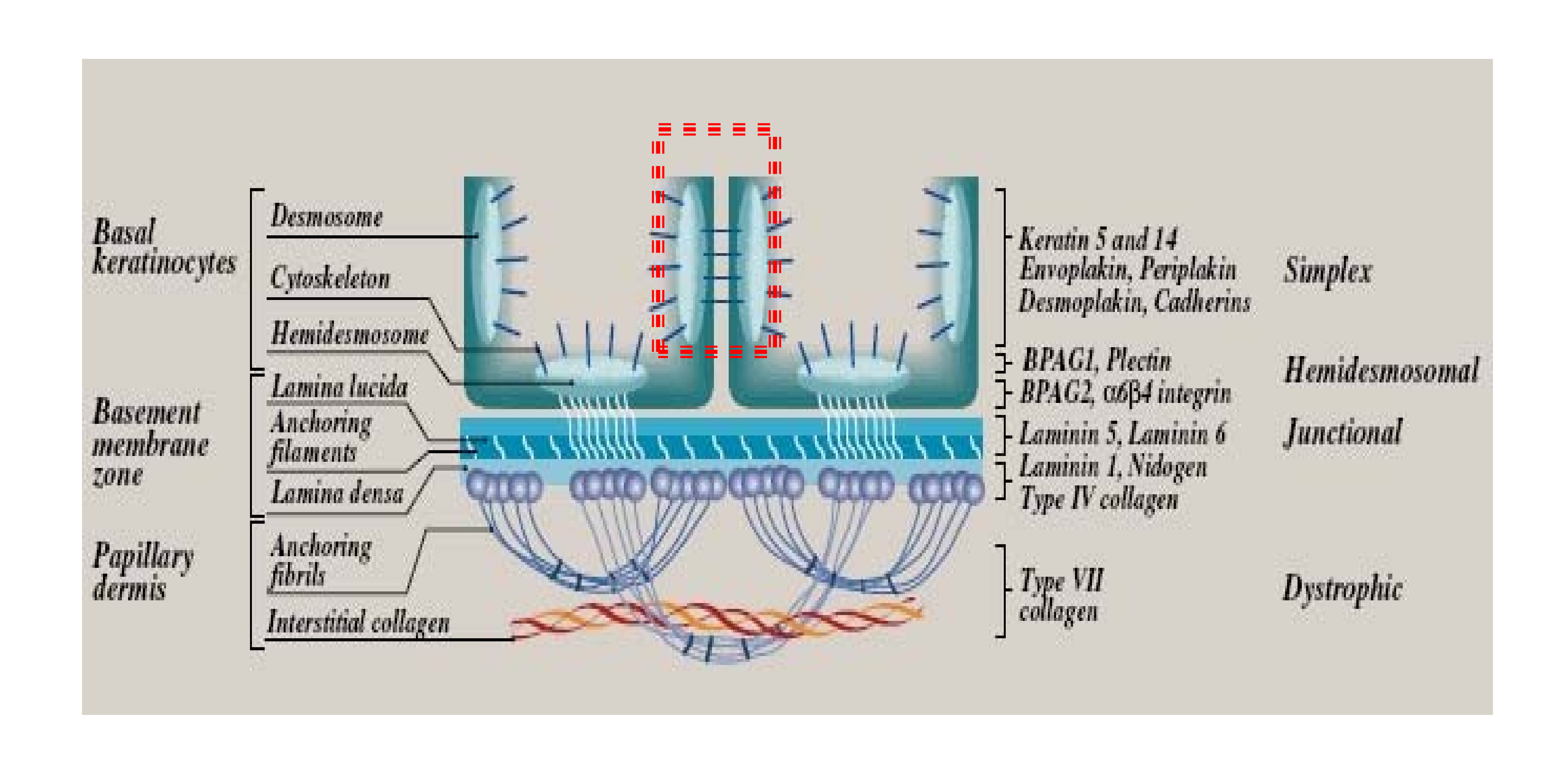

HEMIDESMOSOME
Abs
Abs
BP230
BP180
BP230
Integrin
α6β4
Anchoring
filaments
(laminin-5)
Lamina lucida
(laminins)
Lamina densa
(type IV collagen)
Lamina fibroreticularis
Anchoring fibrils
(type VII collagen)
Interstitial collagen
(Collagen types I and III)

Bullous pemphigoid

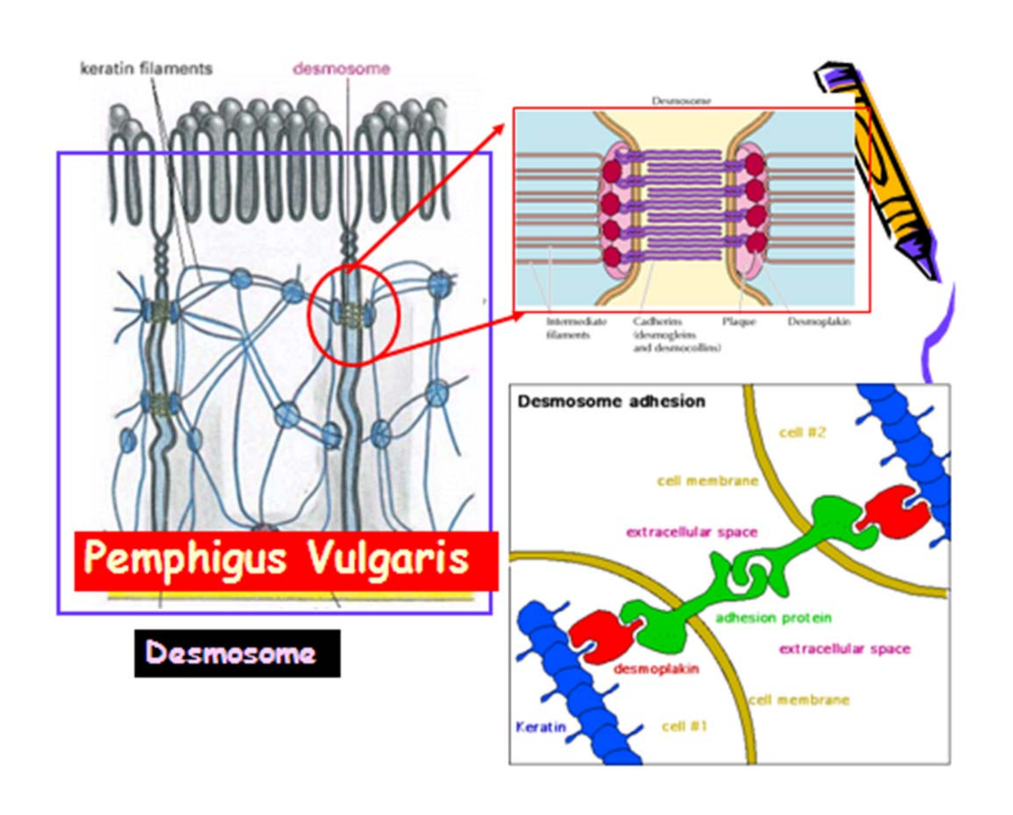
- Bullous pemphigoid is characterized by the presence of immunoglobulin autoantibodies specific for the hemidesmosomal bullous pemphigoid antigens BP230 (BPAg1)

  and BP180 (BPAg2).

Skin Junction



Desmosomal Junction





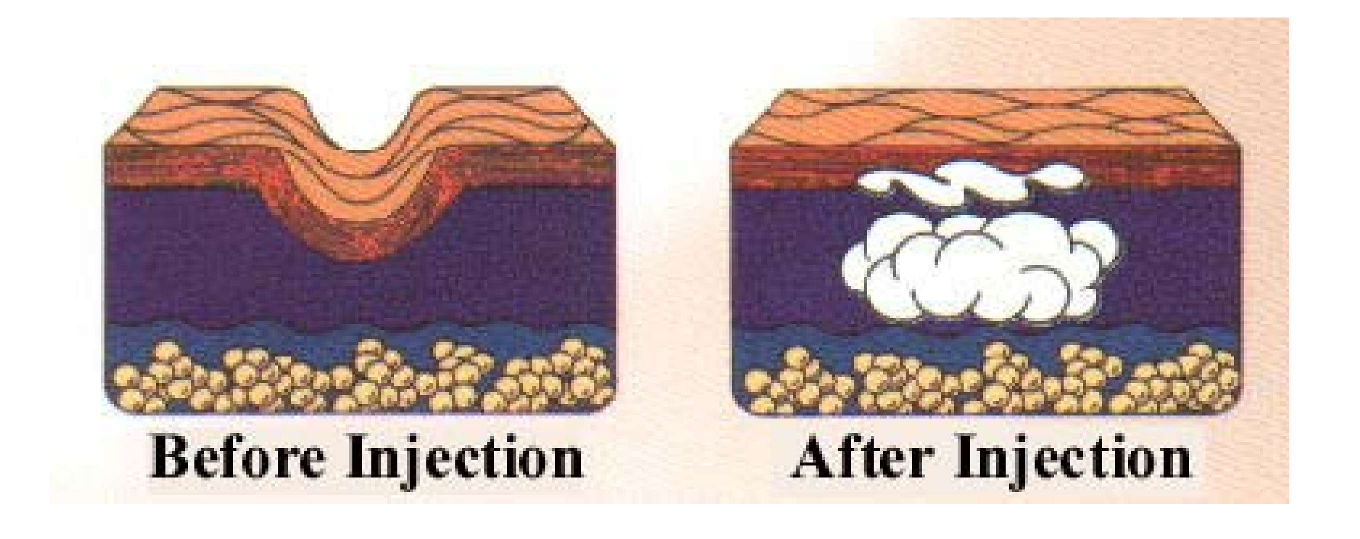
Pemphigus vulgaris There are extensive lesions, mostly erosions and crusts, and no intact bullae.

Disturbed desmosomal adhesion contributes to the pathogenesis of a number of diseases such as pemphigus vulgaris, which is caused by autoantibodies against desmosomal cadherins or viral infection such as herpes simplex infections.

Cosmetic applications of skin biomolecules: anti-wrinkle



Most fillers replace the host components of the skin: collagen, hyaluronic acid, and elastin



Collagen: collagen makes up 75% of our skin protein. From around the age of 25 Collagen levels start to deplete at an astonishing rate of 1.5% every year.

Bovine Collagen Fillers

Bovine collagen is processed from the skin of cows. Approved in the 1980s as a wrinkle treatment, bovine collagen is still widely used as a cosmetic filler.

It can cause allergic reactions, The body naturally breaks down injected collagen, so you need to get collagen injections two to four times per year to maintain results.

Human Collagen Fillers

Human collagen, made from cultures of human cells, became available in 2002. Human collagen causes dramatically fewer allergic reactions than bovine collagen. It is more expensive than bovine collagen, and injections also need to be repeated every three to six months.

Hyaluronic acid:

its molecules bind to water in the skin, hydrating and firming its structure, indicate that HA injections induce collagen production, stimulation of growth factors and inhibition of collagen breakdown, lasting for 4-12 month

Allergic reactions are very rare.

Fat Injection Fillers

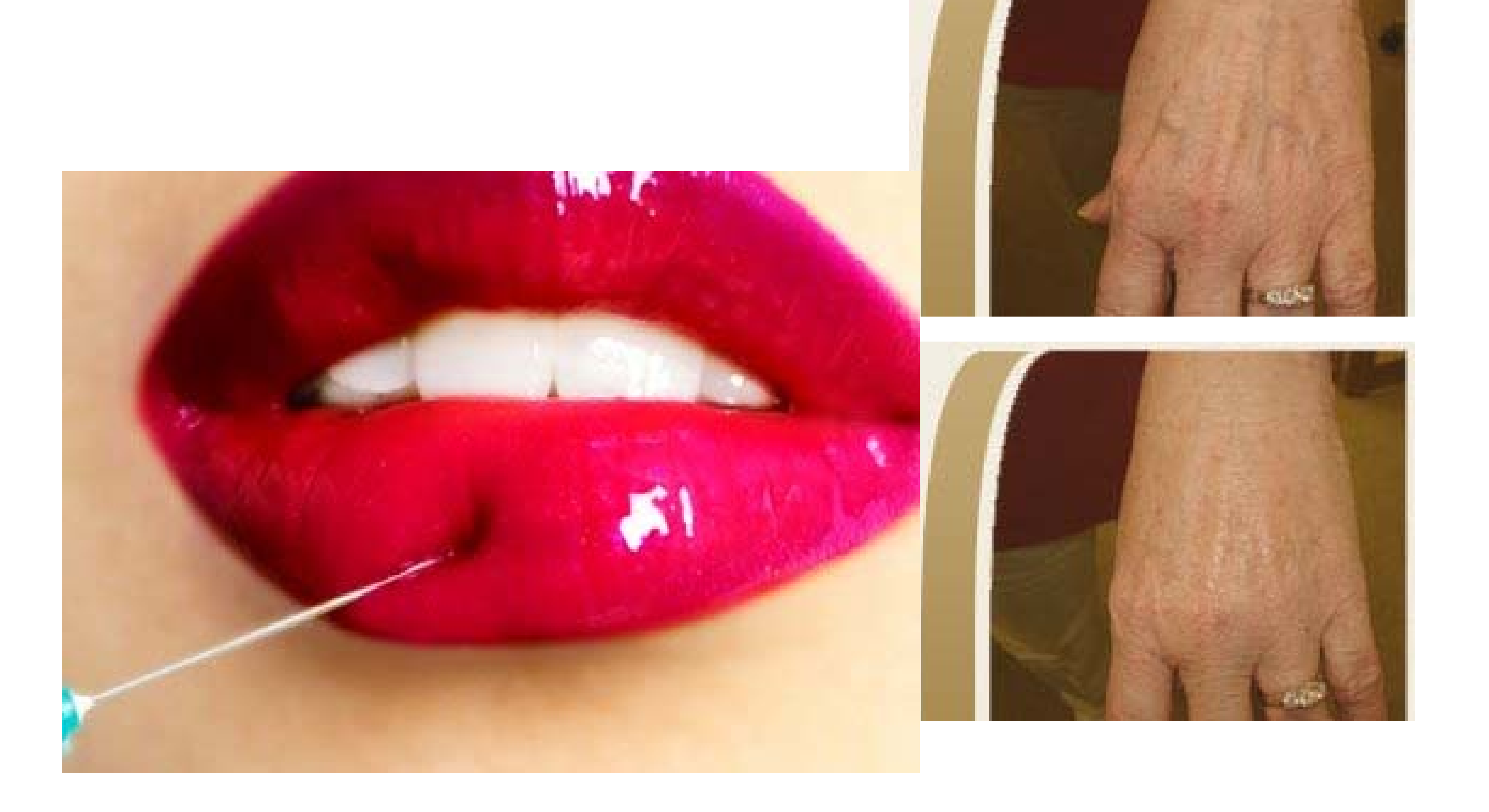
Fat injections involve removing small amounts of fat from the thighs, belly, or buttocks and injecting it under the skin of the face. The fat expands the skin, shrinking wrinkles. Because it is your own tissue, there can be no allergic reaction.


16632


16632'


Before
After


Before
After



Derived from Botulinum toxin type A, **Botox** blocks nerve impulses within facial muscles, thus smoothing wrinkles by temporarily paralyzing the muscles. It is

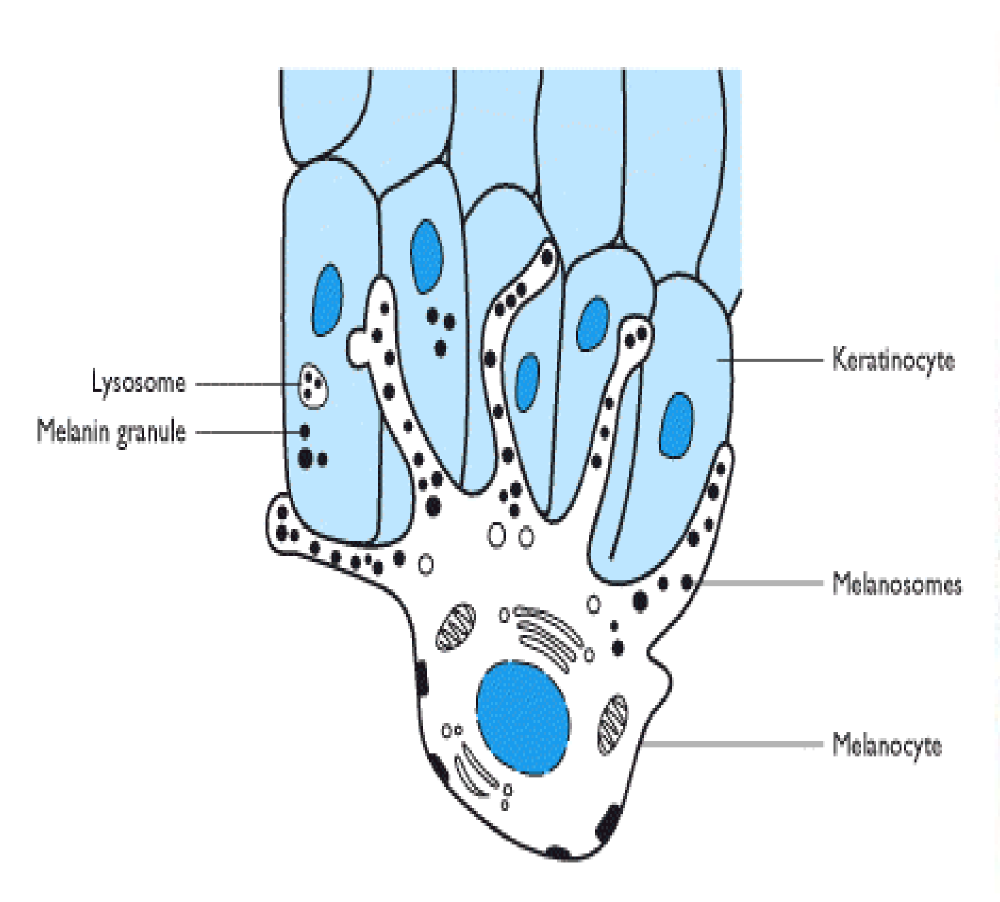


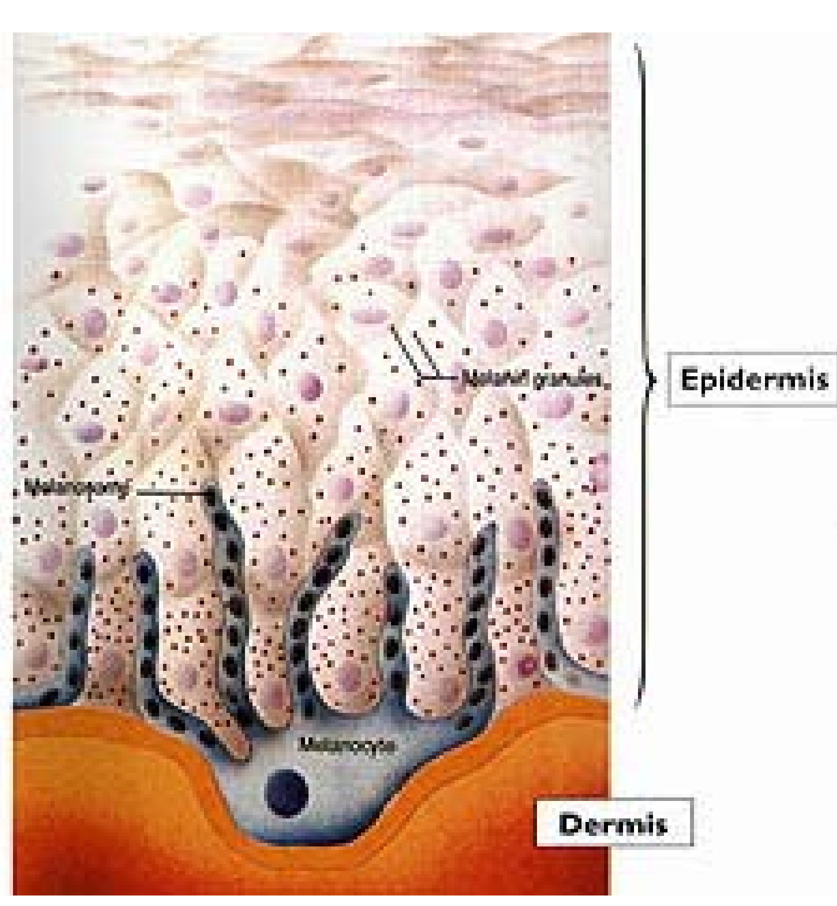
ing use ... **deep lines**
brows ... **ead lines** that
to alw ... ed. It reduces
ice of ... r at the side
It also ... scles which
the e ... me doctors
sfully u ... to lessen the
ll of th ... The process
ten mi ... ections, with
last a ... ths.



tic is a protein that is injected into
elax them, smoothing lines and wrinkles
peated facial movements.

Skin Pigmentation (Melanogenesis)



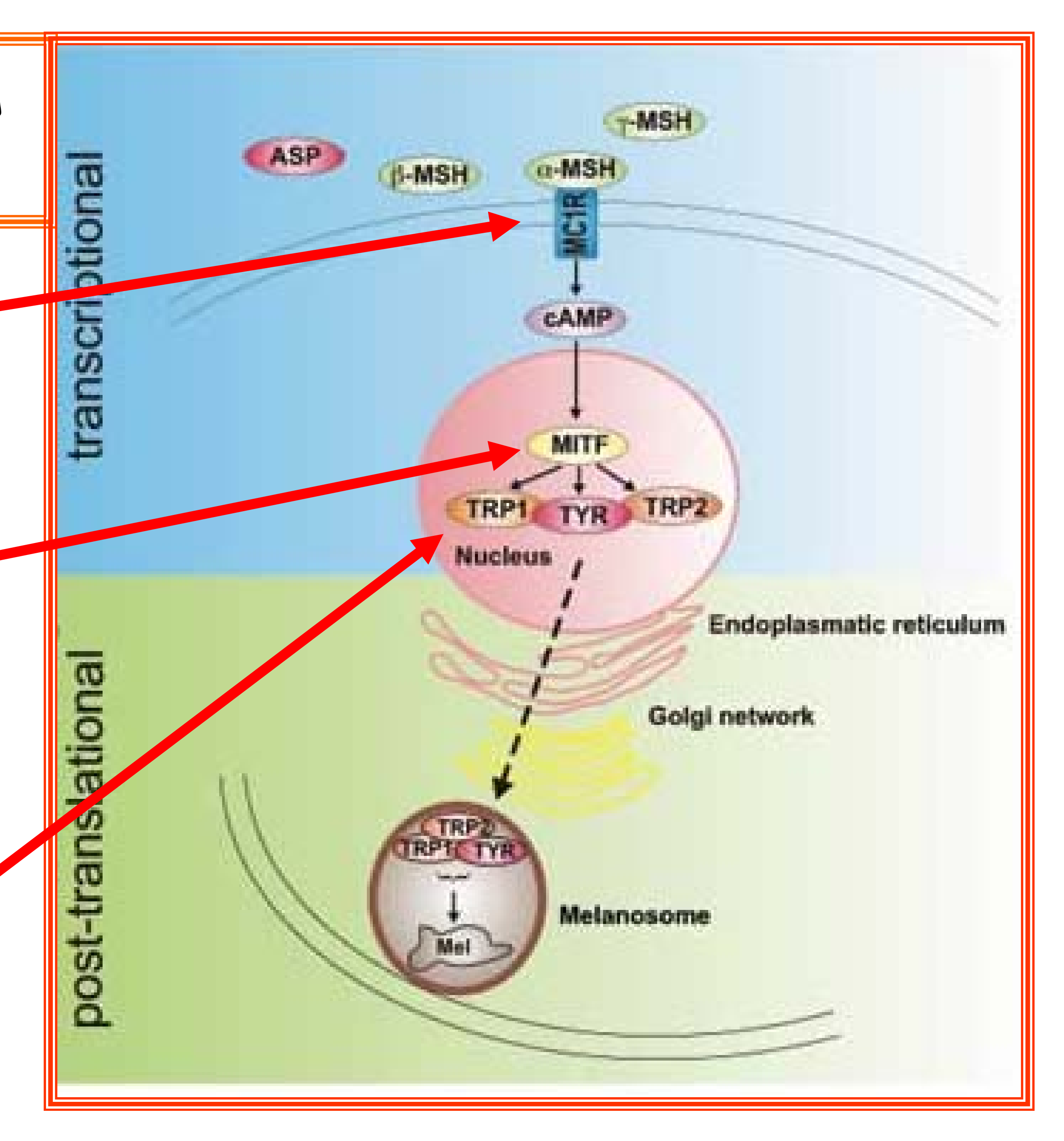


Skin Pigmentation (Melanogenesis)

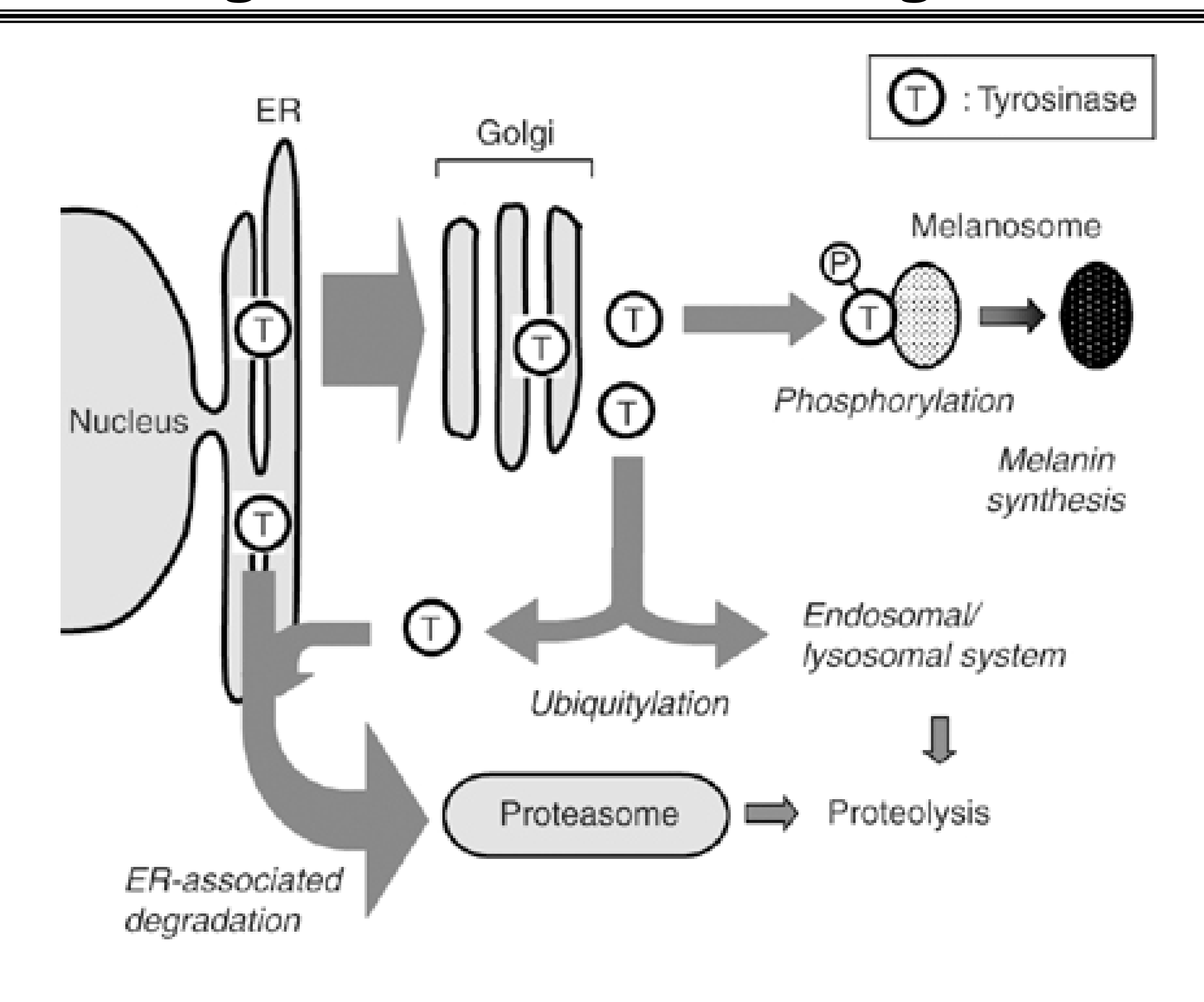
MC1R
(melanocortin-1 receptor)

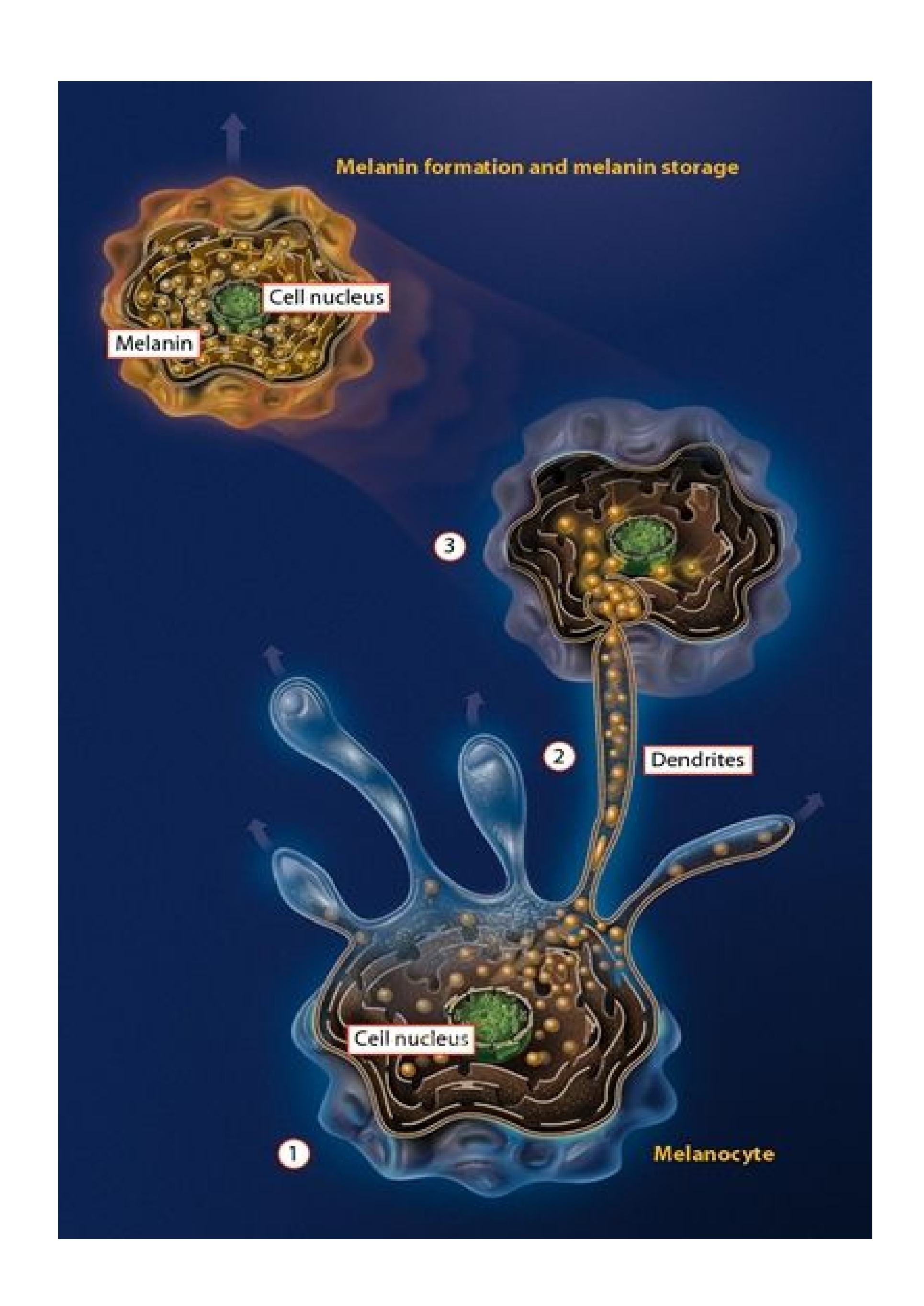
MITF
(microphthalmia transcription factor)

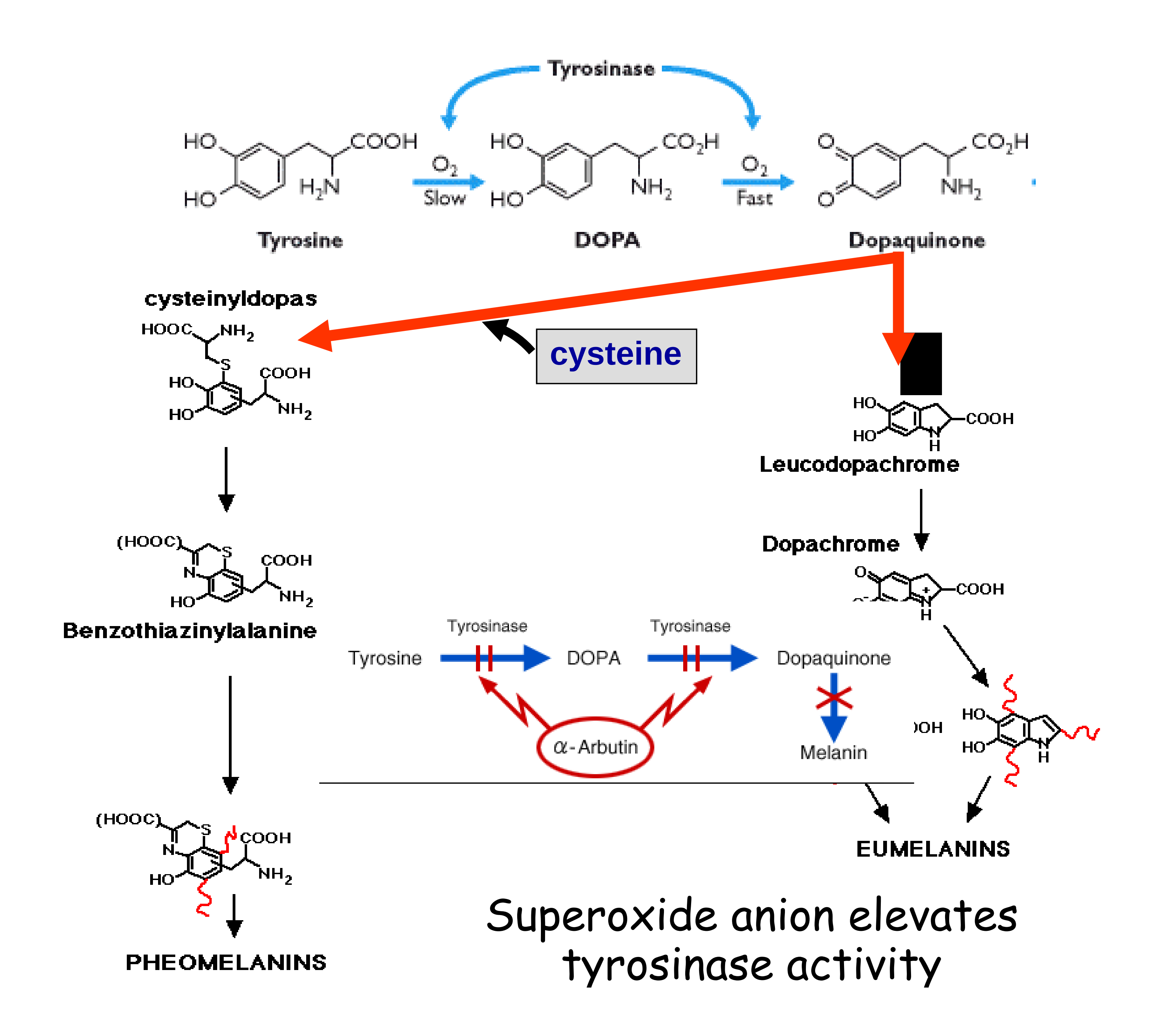
TRYP1:Tyrosinase-related protein 1



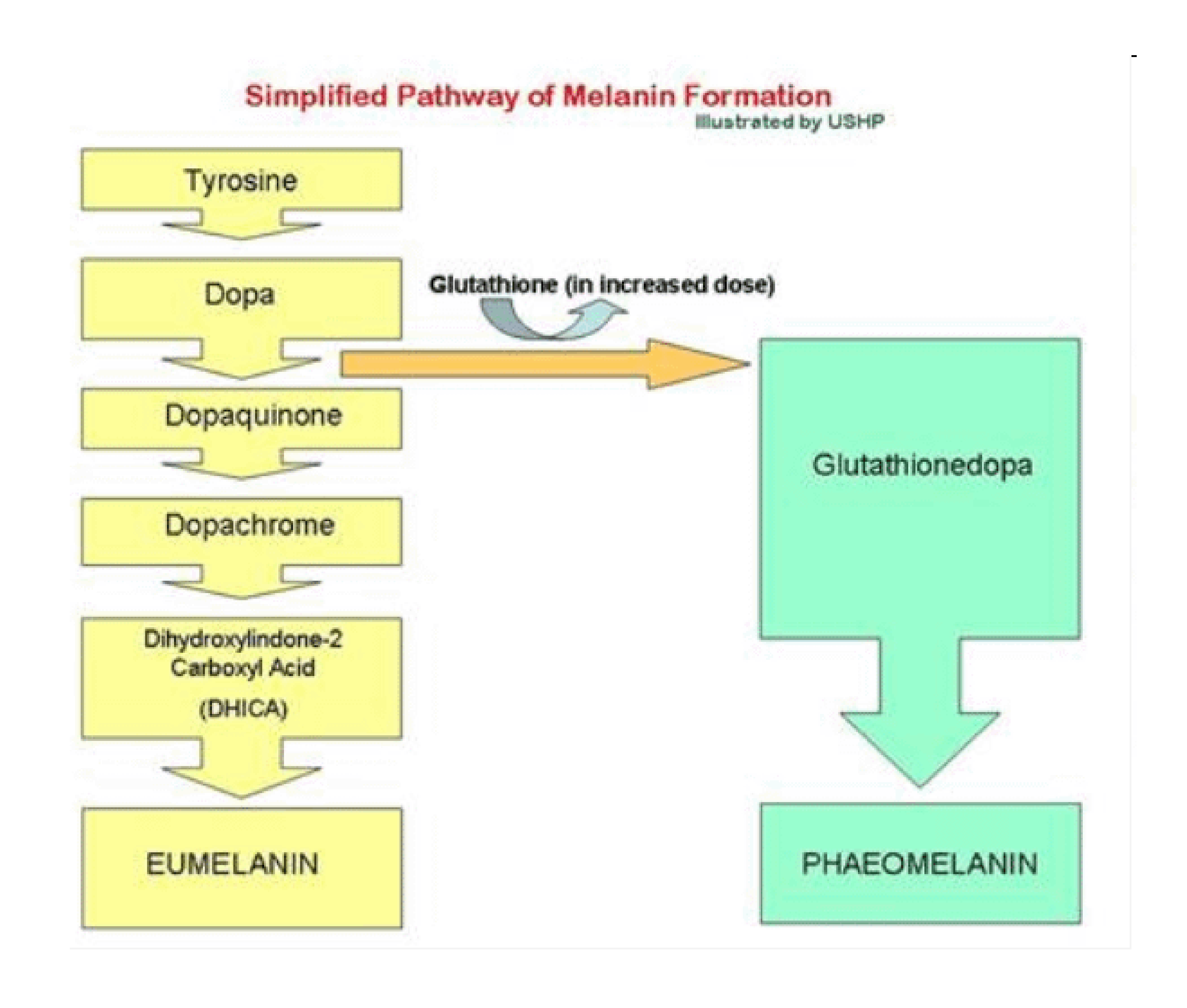
Skin Pigmentation (Melanogenesis)




Melanin formation and melanin storage
Cell nucleus
Melanin
3
2
Dendrites
Cell nucleus
1
Melanocyte



Superoxide anion elevates tyrosinase activity


Simplified Pathway of Melanin Formation
Illustrated by USHP
Tyrosine
Dopa
Glutathione (in increased dose)
Dopaquinone
Glutathionedopa
Dopachrome
Dihydroxylindone-2
Carboxyl Acid
(DHICA)
EUMELANIN
PHAEOMELANIN

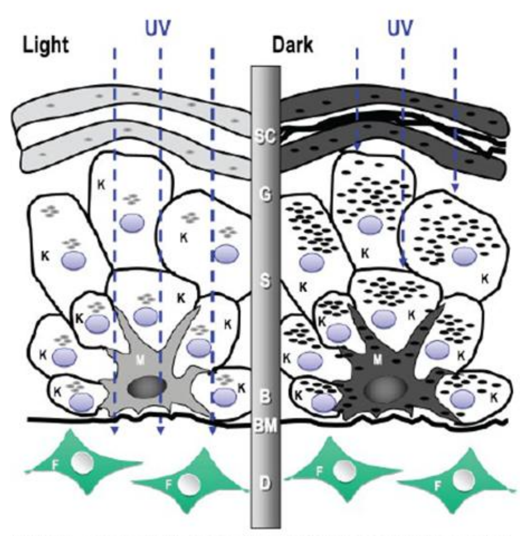
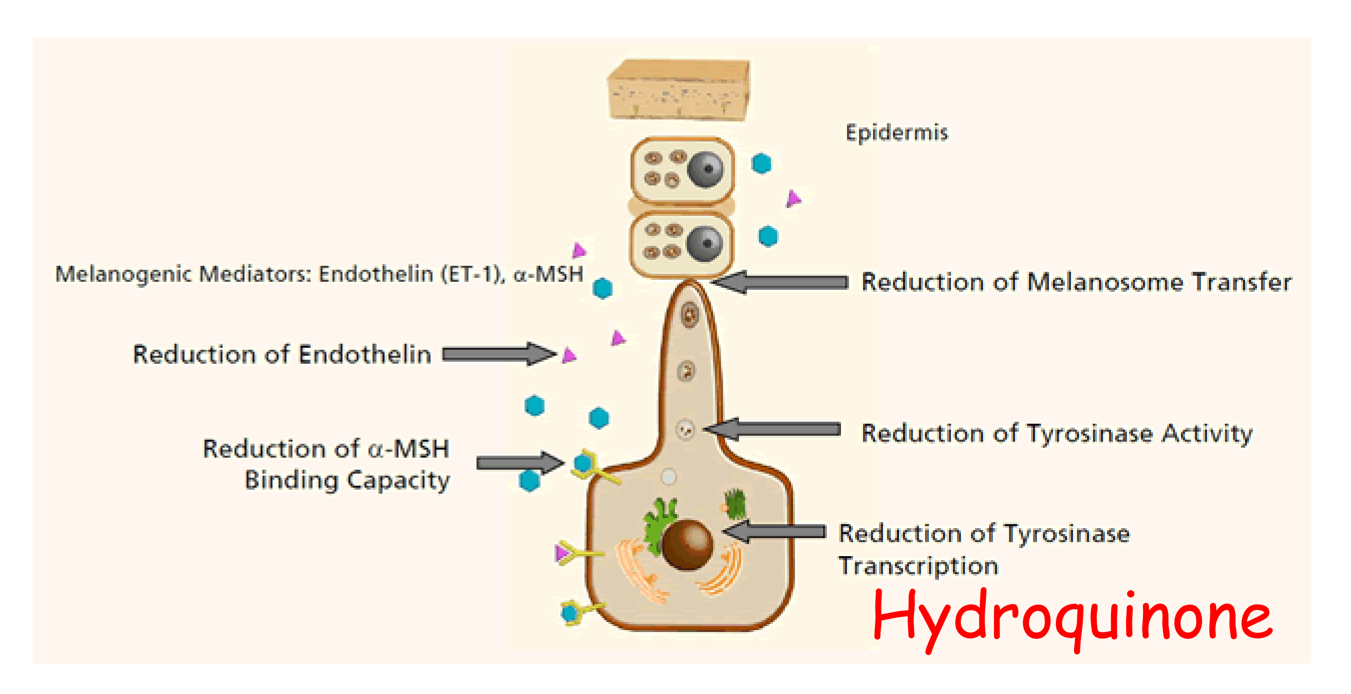


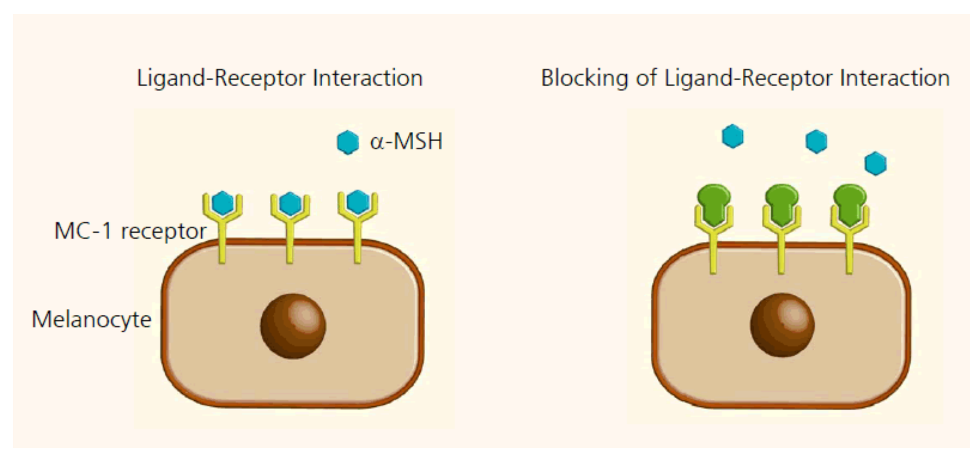
FIGURE 1. **Schematic of human skin architecture from light- and dark-pigmented skin types.** From *top* to *bottom*: *SC*, stratum corneum; *G*, stratum granulosum; *S*, stratum spinosum; *B*, stratum basale; *BM*, basement membrane; *D*, dermis. Cell types: *K*, keratinocyte; *M*, melanocyte; *F*, fibroblast; *shaded oval*, melanin granule

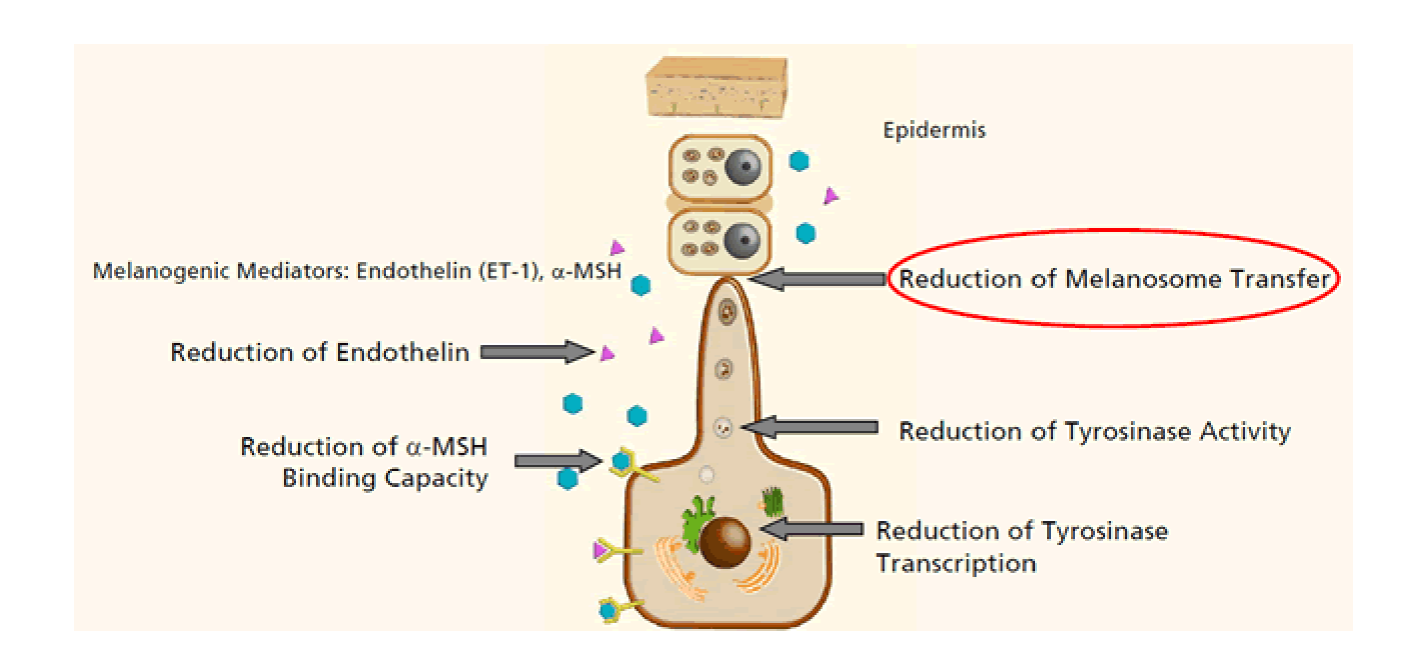
Complexion and biology

	African	Oriental	Caucasian
Type of Melanin Mixture	Pheomelanine / Eumelanine	Pheomelanine / Eumelanine	Pheomelanine / Eumelanine
Proportion of Free Melanin Grains in the Epidermis	Complexed / Free	Complexed / Free	Complexed / Free
Melanine Grain Morphology			
Melanine Grain Size (nm)	1 x 0.5	0.6 x 0.3	0.5 x 0.3

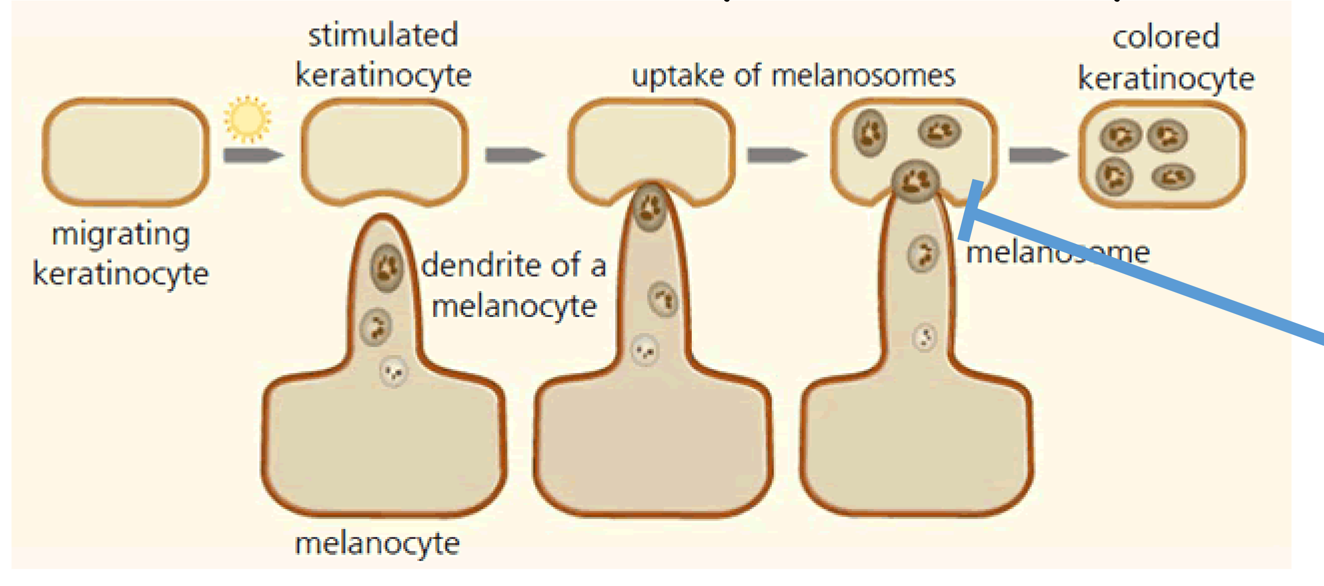
Target mechanism of Whitening agents



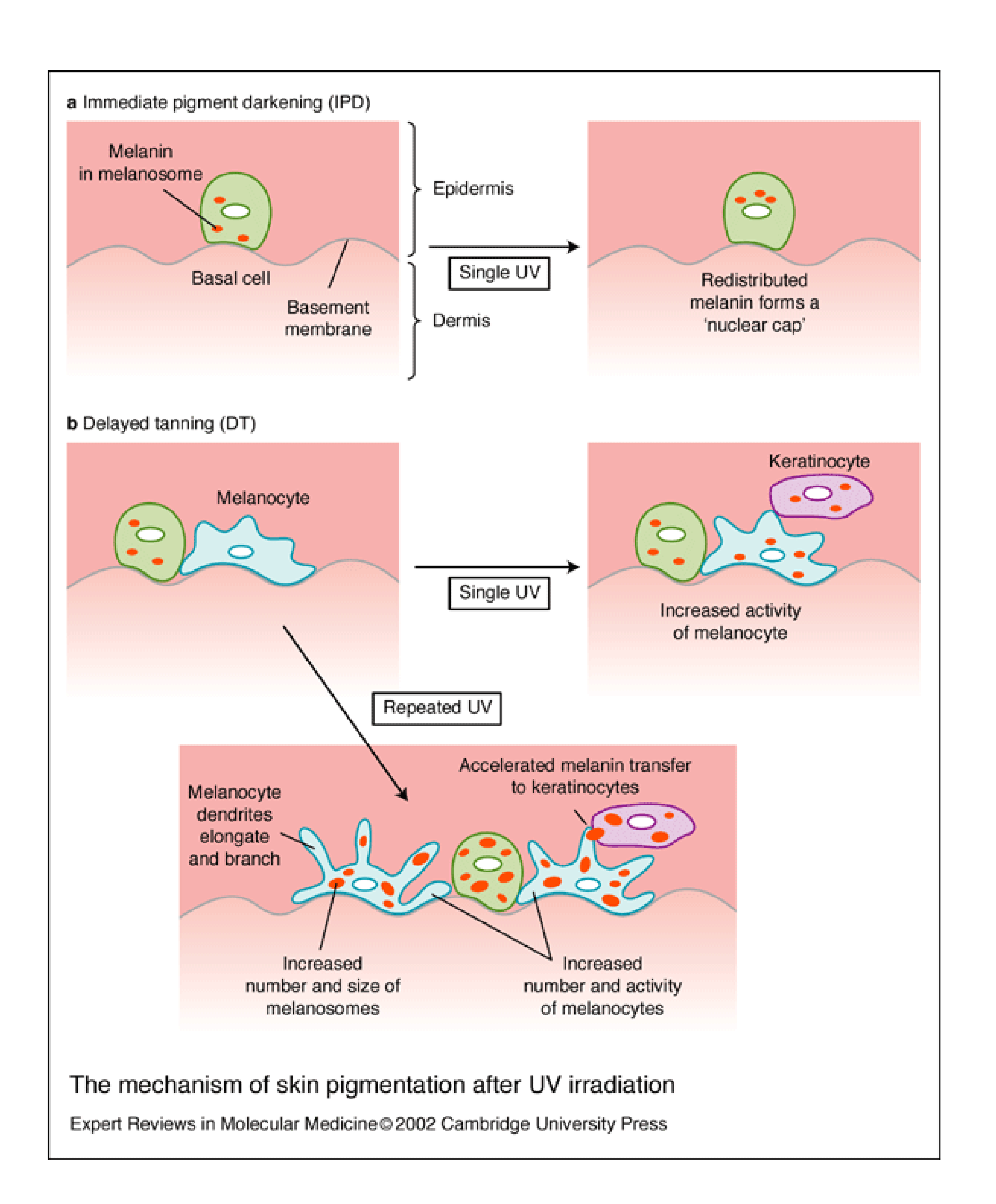




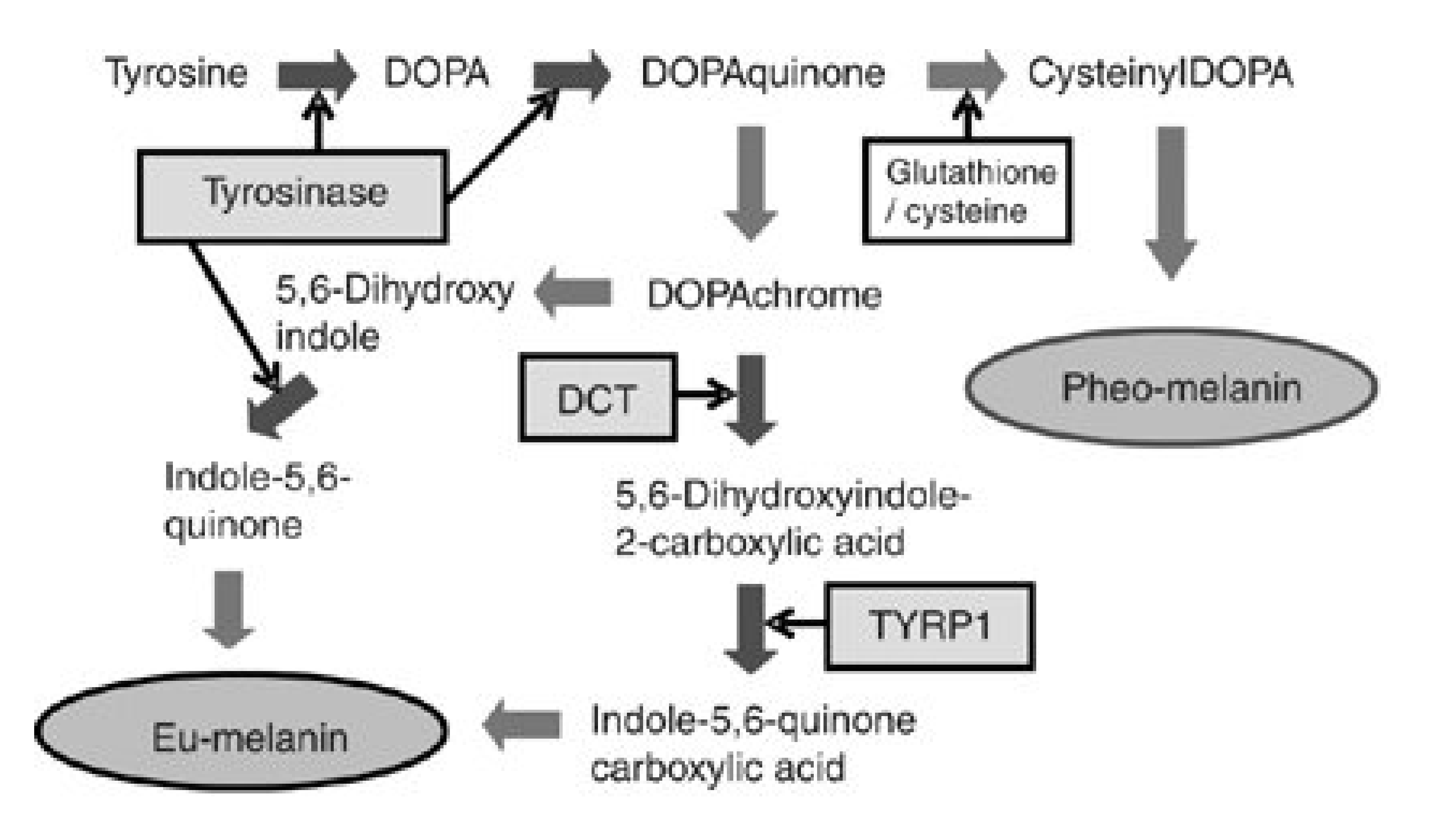
endocytotic activity of keratinocyte



niacinamide

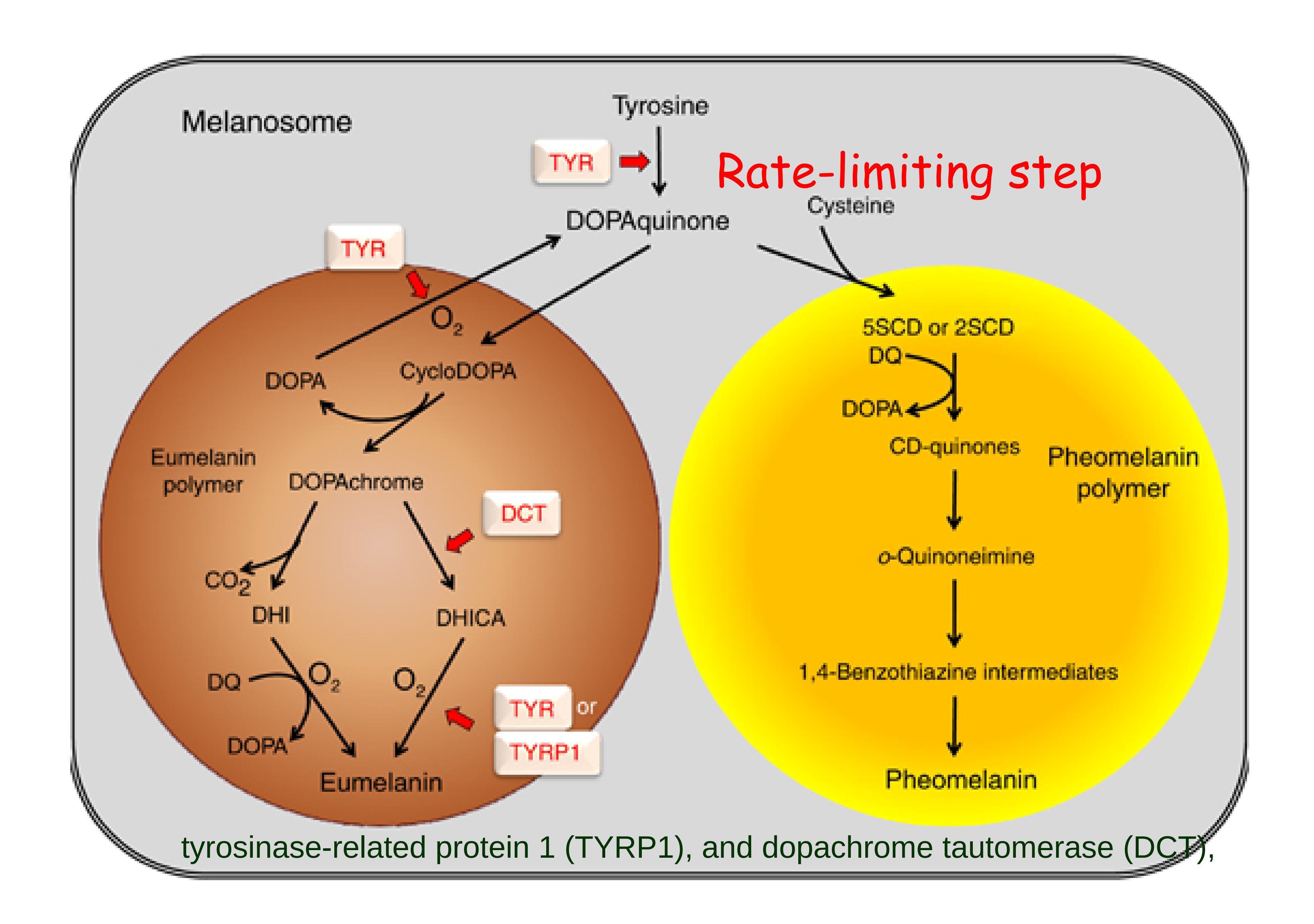


The mechanism of skin pigmentation after UV irradiation

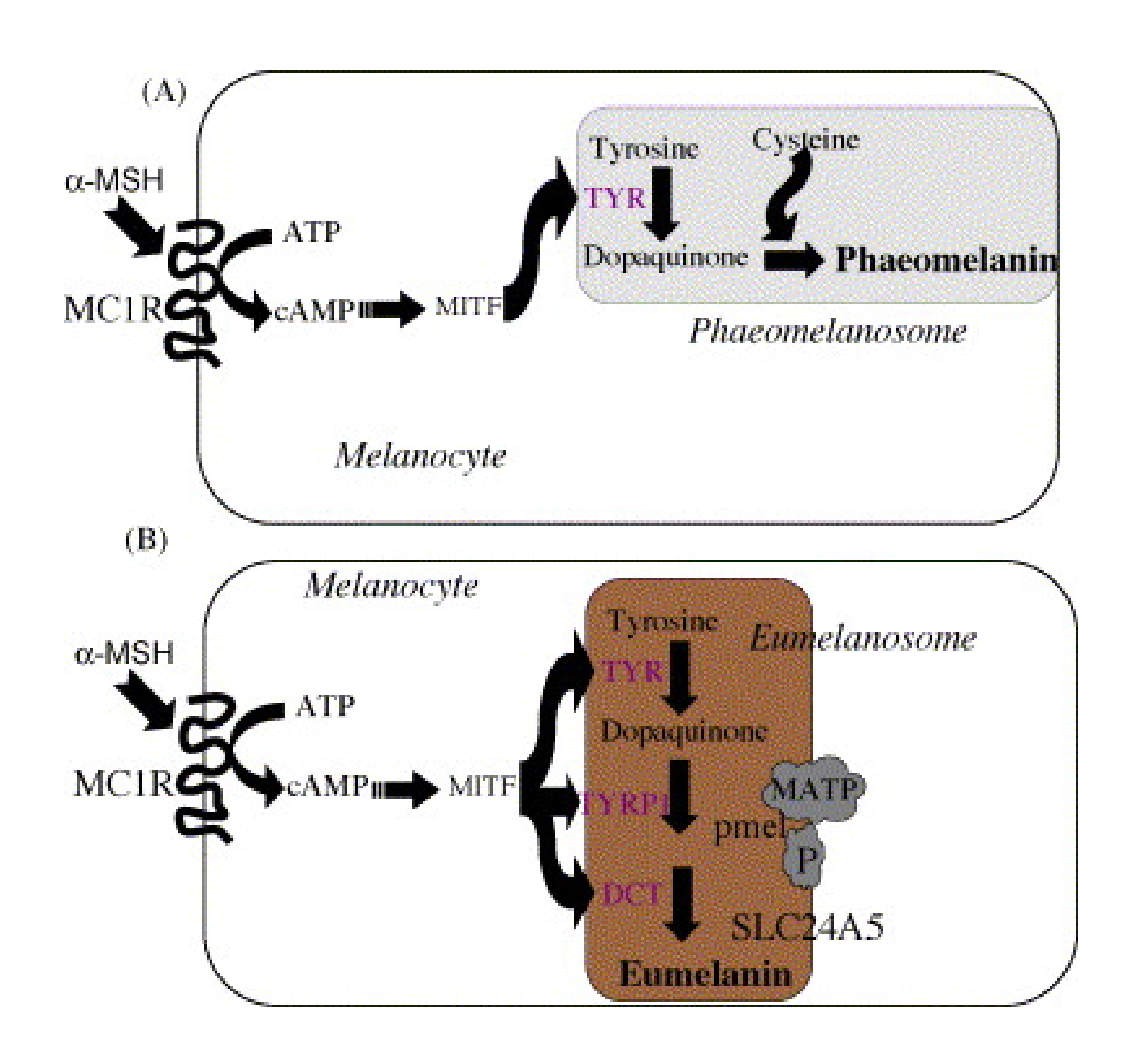


DCT=dopachrome tautomerase
Inhibition by Licorice, Kogic acid, Vit C

TRYP1:Tyrosinase-related protein 1



http://www.nature.com/milestones/skinbio4/full/skinbio20114a.html



(A)
α-MSH
MC1R
ATP
cAMP
MITF
Tyrosine
Cysteine
TYR
Dopaquinone
Phaeomelanin
Phaeomelanosome
Melanocyte
(B)
Melanocyte
α-MSH
MC1R
ATP
cAMP
MITF
Tyrosine
Eumelanosome
TYR
Dopaquinone
TYRP1
MATP
pmel
P
DCT
SLC24A5
Eumelanin

UV-light

Stratum corneum

Free radical

Tyrosinase

Melanin

Basal layer

Melanocytes

Biological Function of Melanin

Melanins function to absorb and disperse UV light and act as free radical scavengers, thus reducing the penetration of UV radiation.

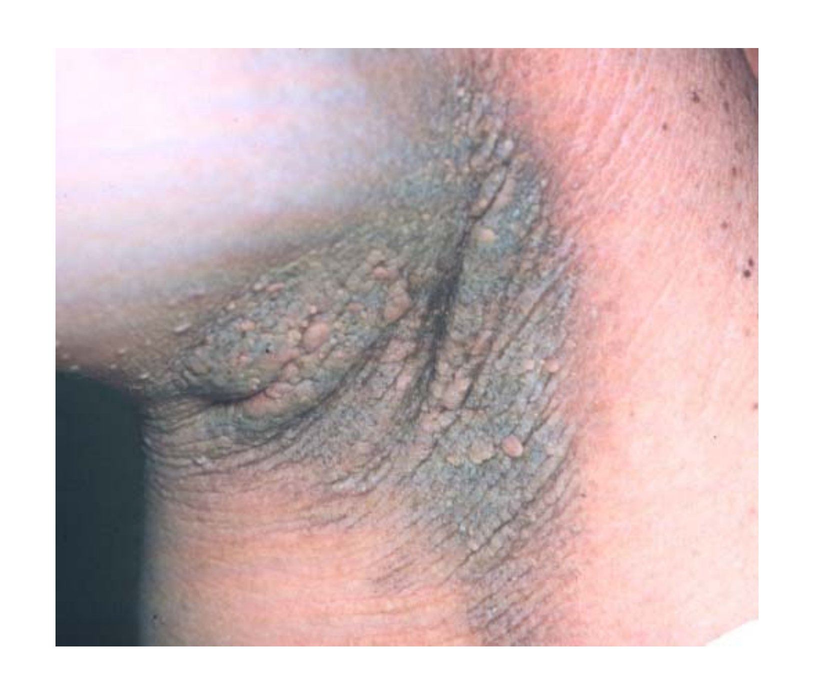
Melanogenesis also serves as a major antioxidant defence mechanism of skin as melanocytes, the specialised cells that produce melanins, neutralise the deleterious effects of active oxygen species and free radicals.

Hyperpigmentation

- Increase in MC-1R on melanocyte membrane
- Increase in MC-1R and melanocyte proliferation
- Activation the mechanism of action of melanogenesis

Hyperpigmentation related diseases

- Acanthosis nigricans
- Cushing's disease
- Addison's disease
- Linea nigra
- Pellagra
- Some cancer drug: cisplatin





Hyperpigmentation in
Acanthosis nigricans
(insulin resistance)





Hyperpigmentation in
Addison's disease
(increase synthesis MSH)





Hyperpigmentation in
Cushing's syndrome
(increase synthesis MSH)




Linea nigra

Post Inflammatory Hyperpigmentation (PIH)

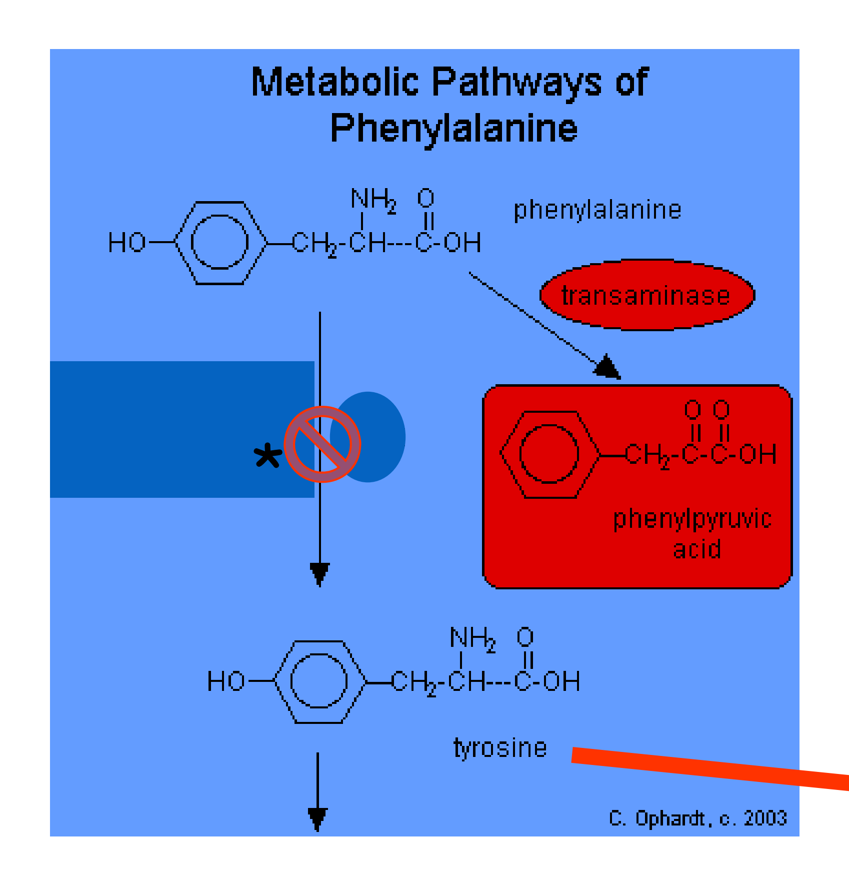


Post Inflammatory Hyperpigmentation (PIH)

after Photodynamic Therapy treatment for acne.

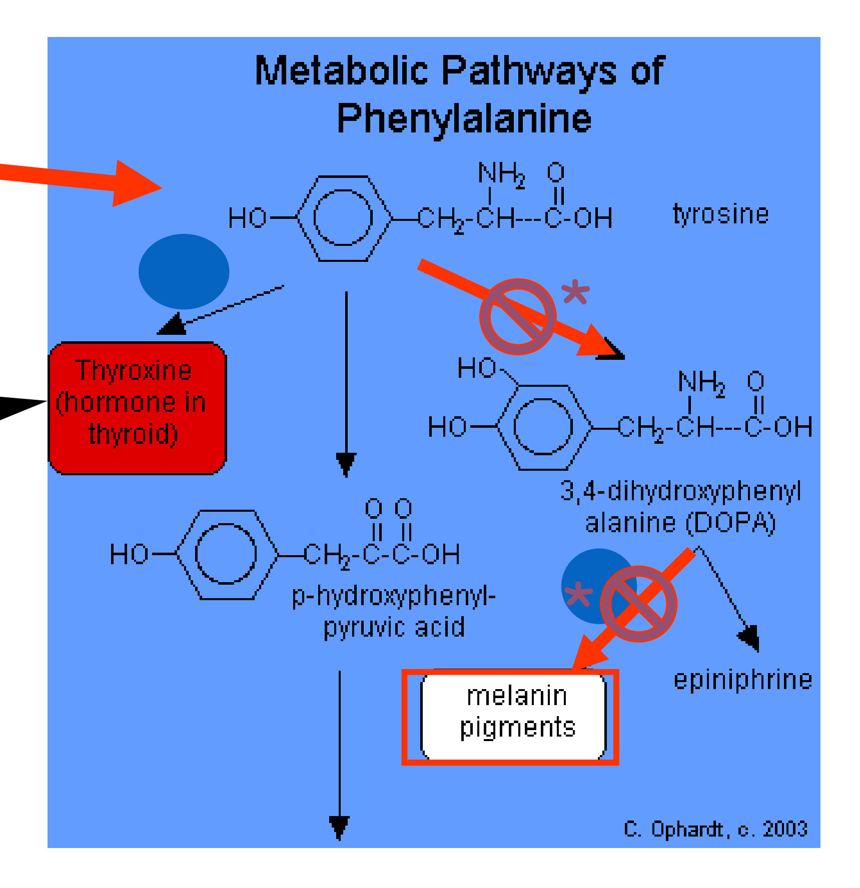
Hypopigmentation

- Decrease in the number of melanocyte
- Lack of tyrosine



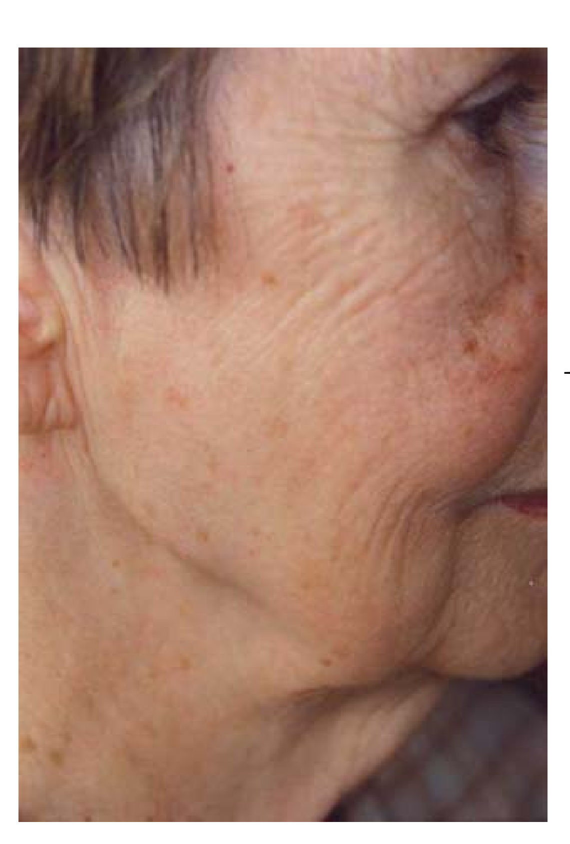
*Phenylalanine hydroxylase (PAH)



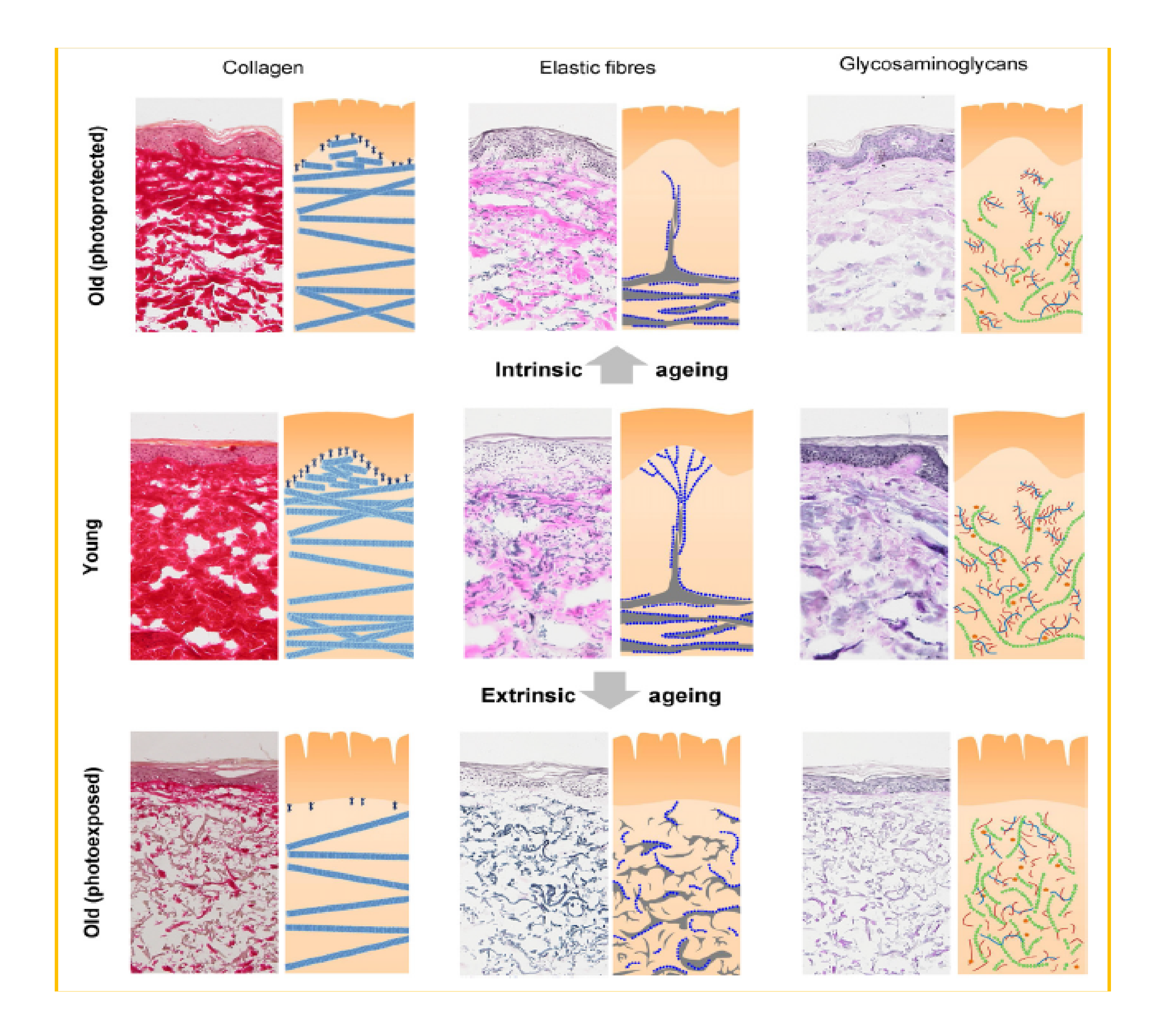


* tyrosinase

Biochemistry of Skin Aging

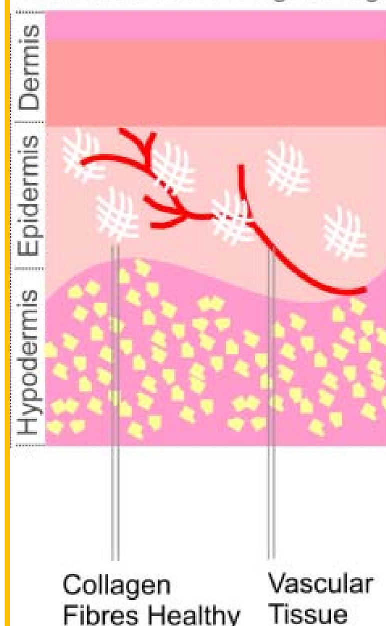


- Intrinsic Aging
- Extrinsic or photo aging


Collagen
Elastic fibres
Glycosaminoglycans
Old (photoprotected)
Intrinsic
ageing
Young
Extrinsic
ageing
Old (photoexposed)

20s

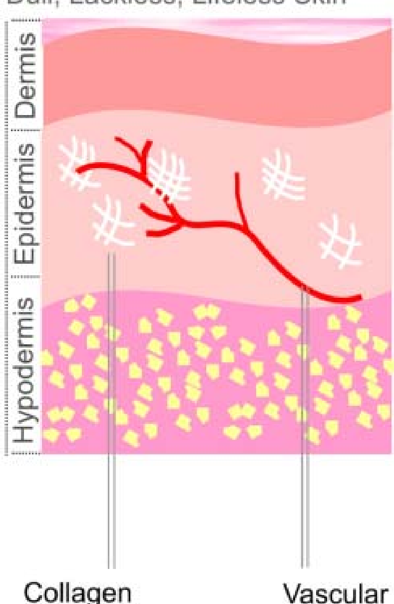
Free Radicals Attack Surface
Environmental Damage is High



Constant exposure to the sun & fast life style leads to skins premature aging.

30s

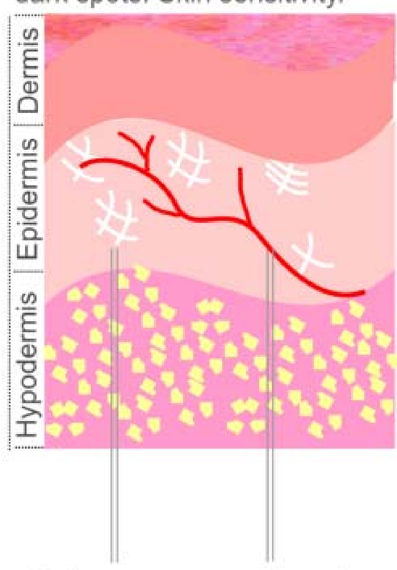
First Signs of Aging Appear
Dull, Lackless, Lifeless Skin



Skin regeneration is reducing leading to dull complexion & uneven skin tone. Use of harsh skin care can become apparent. Elastin degradation can show first signs of aging.

40s

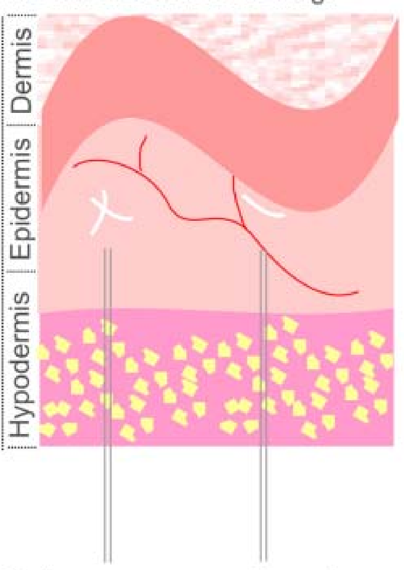
Significant dullness, aging & dark spots. Skin sensitivity.



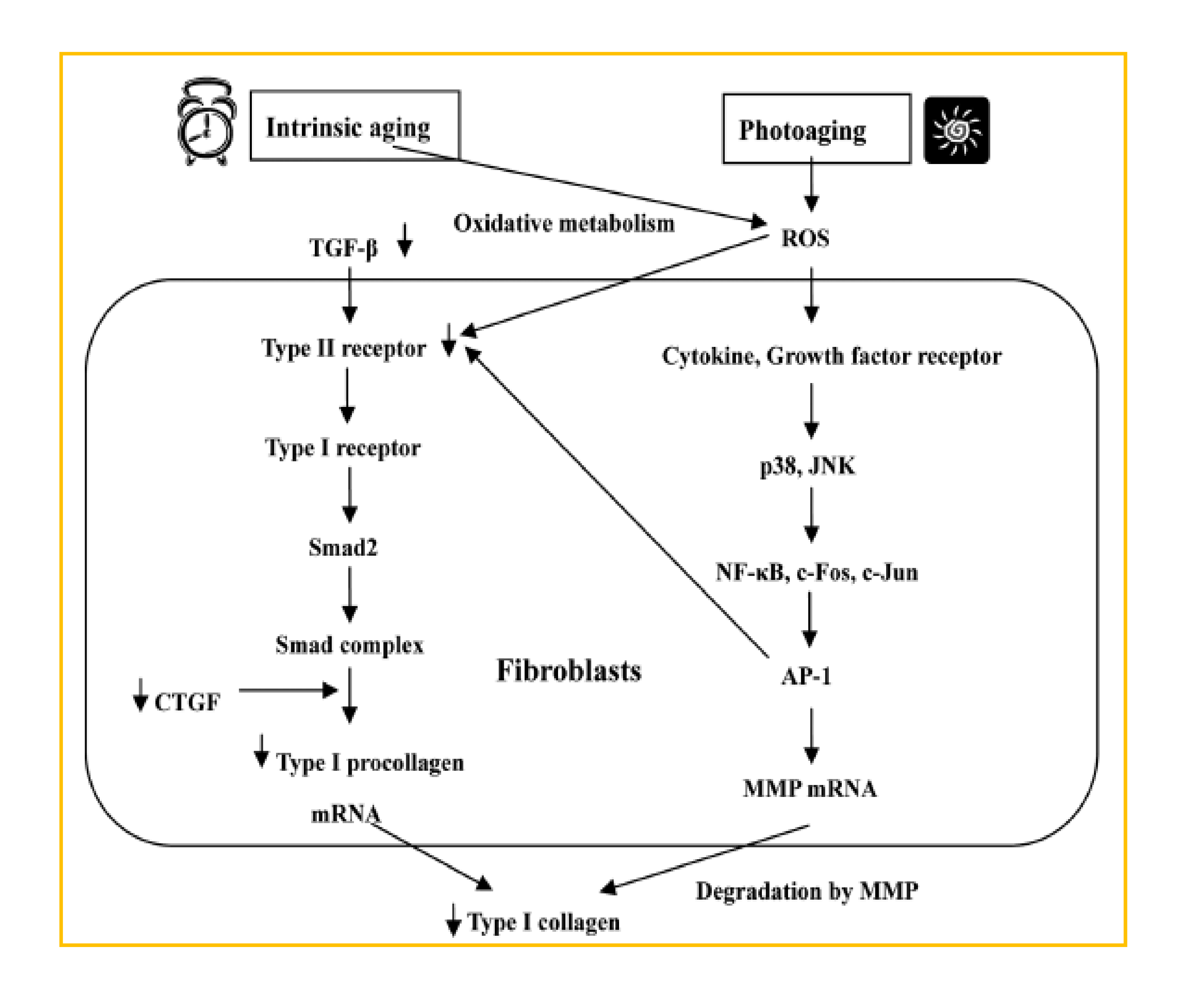
Skin thinning can cause sensitivity, redness, dry, oily, sudden redness. Photo aging appears - dark spots - more prominent signs of aging appear.

50+

Significant tension decrease.
Moisture retension slowing.



Decrease in surface tension impairs skin structure and ability to defend itself. Barrier lessens leading to less efficiency in retaining moisture. Combined with excessive dryness sometimes accompanied by adult acne.



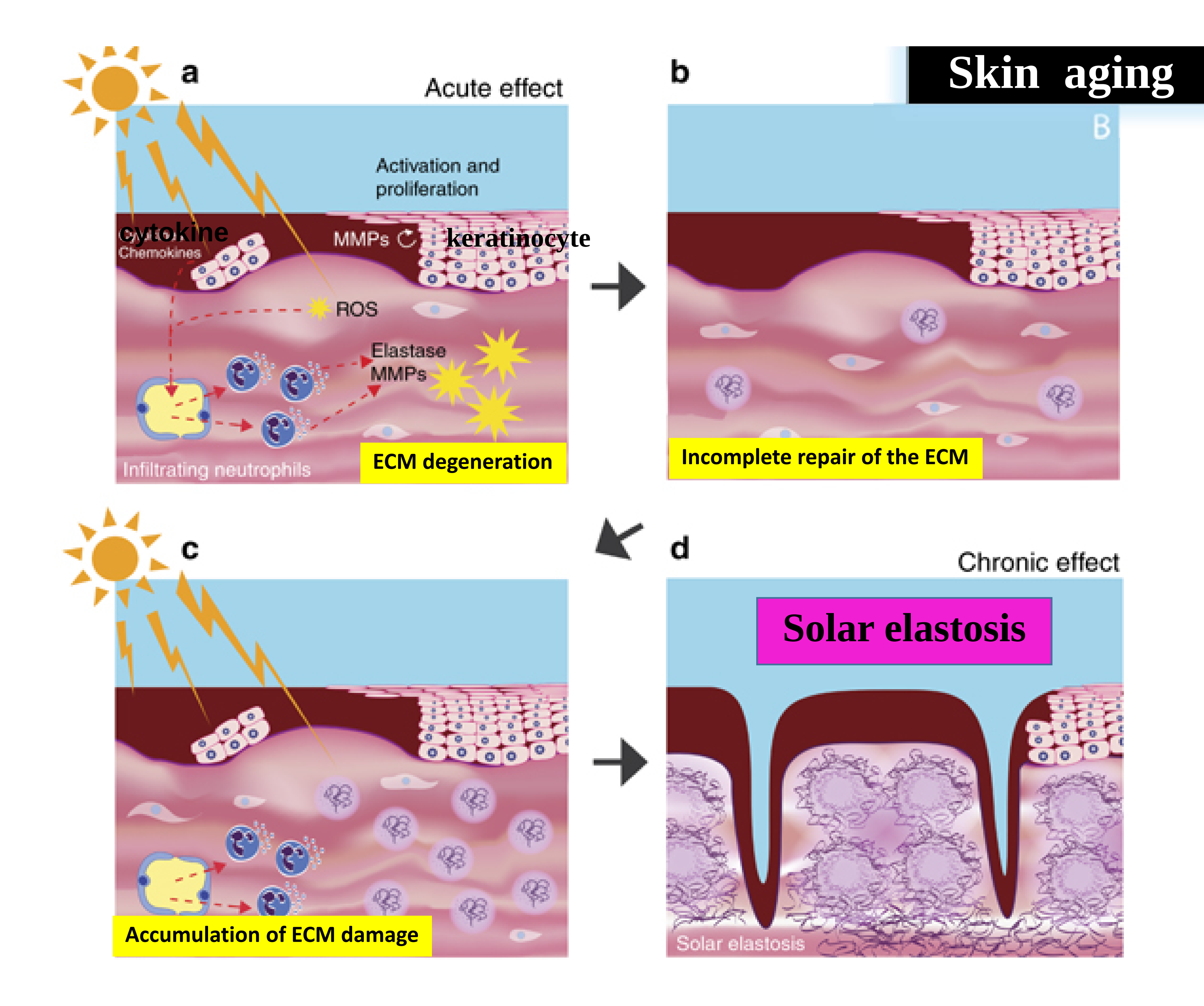
Intrinsic aging
Photoaging
Oxidative metabolism
ROS
TGF-β
Type II receptor
Cytokine, Growth factor receptor
Type I receptor
p38, JNK
Smad2
NF-κB, c-Fos, c-Jun
Smad complex
Fibroblasts
AP-1
CTGF
Type I procollagen
mRNA
MMP mRNA
Degradation by MMP
Type I collagen

Biochemistry of Skin Aging

Effects on cells → Decrease in cell apoptosis

Effects on skin ECM

- Effects on proteins
- Effects on lipids
- Effects on DNA
- Effects on proteoglycans and GAGs


Skin aging
a
Acute effect
Activation and proliferation
cytokine
Chemokines
MMPs
keratinocyte
ROS
Elastase
MMPs
Infiltrating neutrophils
ECM degeneration
b
Incomplete repair of the ECM
c
Accumulation of ECM damage
d
Chronic effect
Solar elastosis
Solar elastosis

Exogenous / Endogenous

STRESS

Proteins

Oxidatively modified proteins

Protein turnover

Decrease of proteasome activity

Protein synthesis

Hydroxynonenal protein adducts

Glycation

Advanced Glycation Ends products

(AGEs)

Exogenous / Endogenous

STRESS

DNA

Telomerase interactions

DNA-Protein cross links

Mitochondrial DNA common deletion

Decrease of DNA repair mechanisms

- base excision repair

- nucleotide excision repair

8 oxoguanine

Accumulation in mitochondrial DNA

Mitochondrial dysfunction

Energetic Crisis

Immune system

Thymine derivatives

DNA replication

Altered Transcription

Genome instability

Nutrition and Skin







EFA



Water



Minerals

Proteins



Vitamins









Pellagra:
Niacin def.

Pellagra



Vitamin B3, also known as Niacin or Nicotinic acid, is a water-soluble B-vitamin that plays a significant role in energy metabolism and maintaining healthy skin .

Niacin is synthesized inside the body by the liver from the essential amino acid tryptophan.

Niacin is lost with cooking. Also, alcohol inhibits vitamin B3 absorption.

*Corn is the only grain low in niacin.



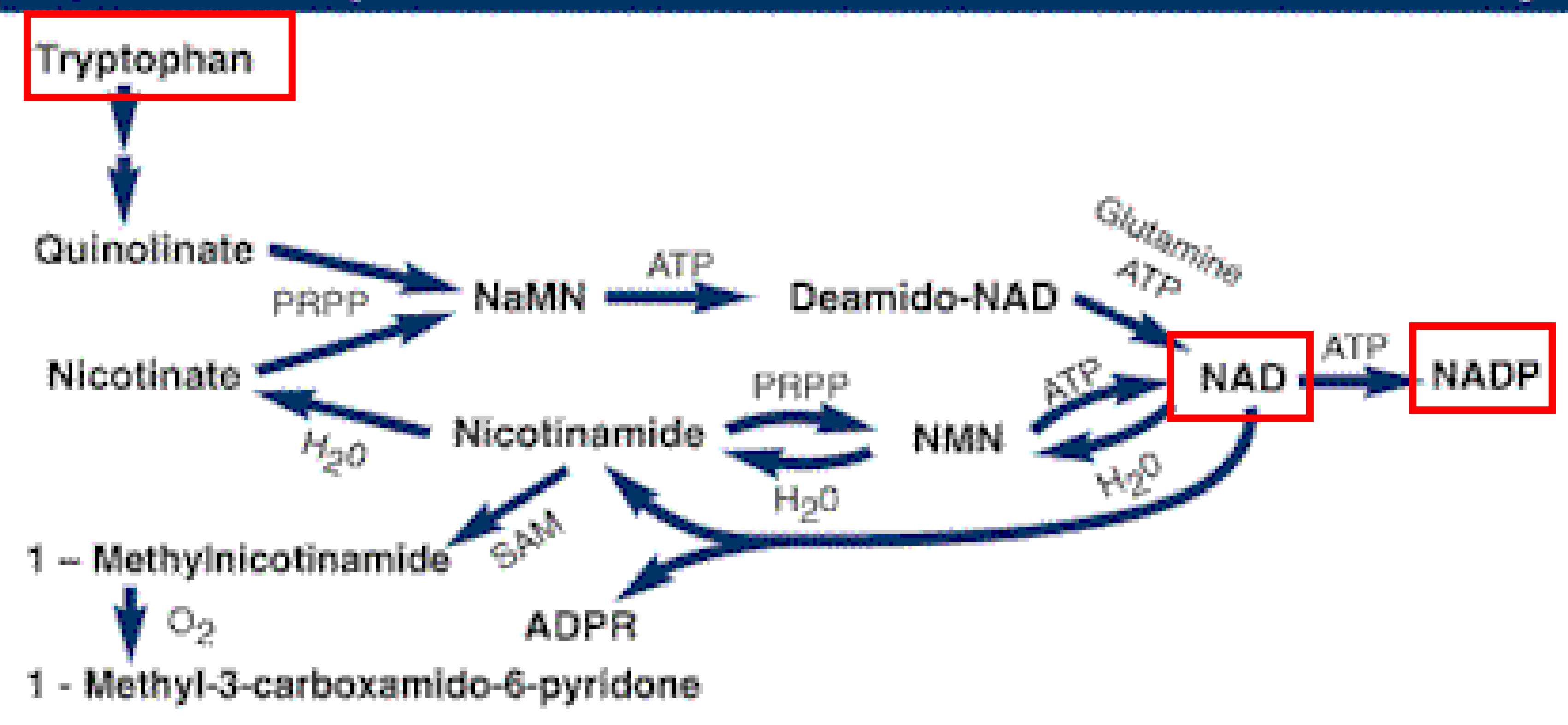


Fig. 1: Principle Action of B3 Metabolism in the Body
Tryptophan
Quinolinate
PRPP
NaMN
ATP
Deamido-NAD
Glutamine
ATP
NAD
ATP
NADP
Nicotinate
H20
Nicotinamide
PRPP
NMN
ATP
H20
H20
SAM
1 – Methylnicotinamide
O2
ADPR
1 - Methyl-3-carboxamido-6-pyridone

Deficiency of vitamin B
(Vit B2, Vit B5, Vit B9 or vit B12)

- hair changes, and recurrent angular stomatitis









Hair loss (alopicia)
caused by biotin (vit B7) deficiency

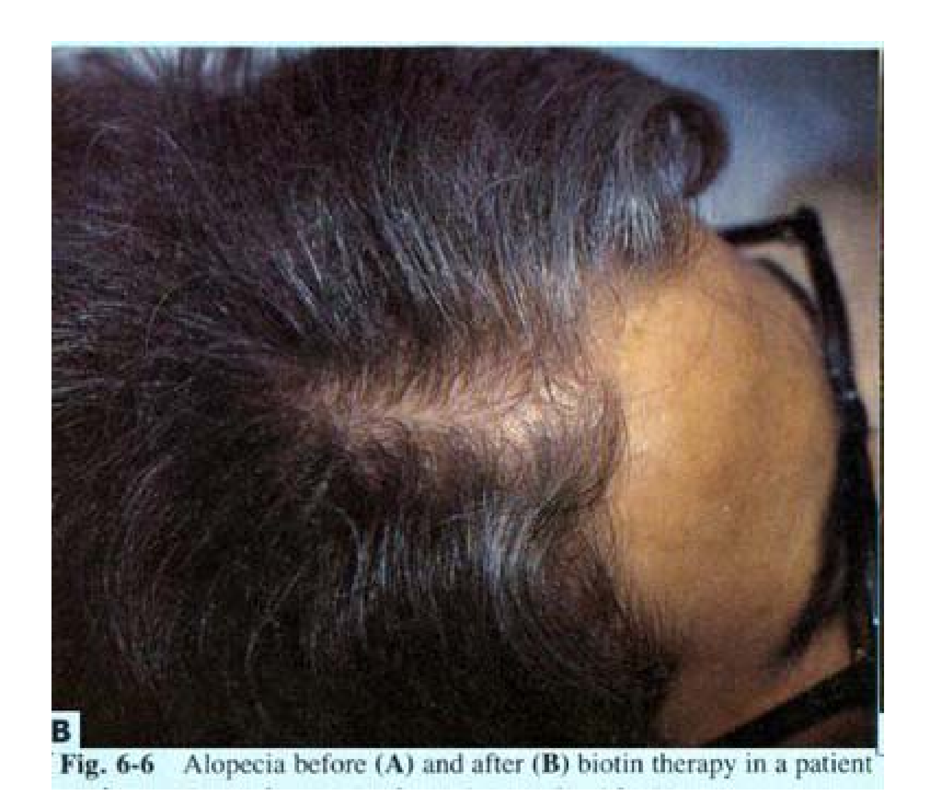
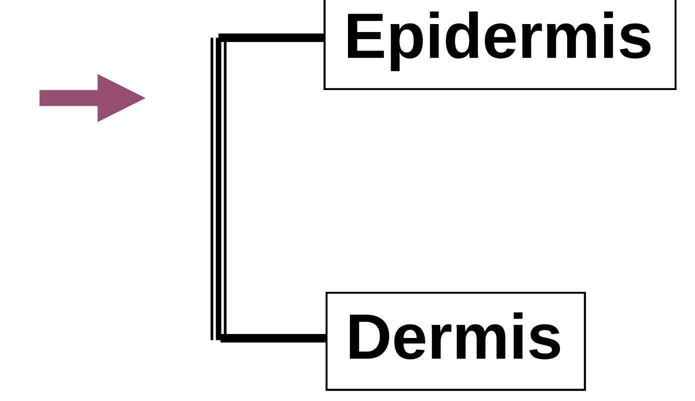


Fig. 6-6 Alopecia before (A) and after (B) biotin therapy in a patient

Objective

- Structure and Function of skin biomolecules



- Skin junction and diseases
- Skin Melanogenesis: mechanism and functions
- Skin Melanognesis and associated disorders
- skin ageing
- Nutrition and skin